Exhibit 46

Hysterosalpingo-Radionuclide Scintigraphy (HERS)

Mario Iturralde and Pieter Ferdinand Venter

A radionuclide procedure, hysterosalpingo-radionuclide scintigraphy (HERS), was designed to evaluate the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries as well as to image and functionally outline the patency of the pathways between these two extremes of the female reproductive system. Technetium-99m human albumin microspheres (^{99m}Tc-HAM) were deposited in the posterior fornices of patients who were divided into two specific groups. Group I consisted of patients who were to undergo different elective gynecologic operations, in which besides obtaining sequential images, radioactivity levels were measured in the removed organs and tissues. Group II consisted of patients referred by the Infertility Clinic for evaluation of their reproductive system pathways patency. In this latter group, HERS was compared with contrast hysterosalpingography (HSG) and peritoneoscopy (PCP). The results obtained from measurements of radioactivity levels on the removed surgical specimens and comparison with other conventional gynecologic diagnostic procedures provide accurate evidence of the migration of ^{99m}Tc-HAM from the vagina, through the uterus and tubes, to the peritoneal cavity and ovaries, and show that HERS is a simple noninvasive method for functionally imaging and assessing the patency of the female reproductive system pathways.

IN THE adult female, the peritoneal cavity communicates with the outside via the fallopian tubes, the uterus, and the vagina and there is evidence for the migration of different substances in either direction (Fig. 1). For example, malignant cells from ovarian carcinoma can be demonstrated in the posterior fornix of the vagina.[1] After menstruation, the gonococcus can penetrate the cervix and gain access through the uterus and tubes to the peritoneal cavity and ovaries.[2] Retrograde menstruation is also a well known phenomenon. For pregnancy to occur, spermatozoa have to move up the uterus as the ova moves down the tube. After insufflation, air and gases pass easily from the vagina into the peritoneal cavity up to the diaphragm. Radioopaque contrast media are introduced with great ease through the uterus and tubes into the peritoneal cavity, and tubal patency is easily demonstrated during peritoneoscopy by injection of a dye through the cervix and into the tubes.

If transit can take place so easily, it is probable that the same happens with chemical substances used for hygienic, cosmetic, or medicinal purposes, many of which may have potential carcinogenic or irritating properties (Table 1). Such migration could well explain the etiologic role of chemical substances in certain gynecologic diseases, and specially in carcinoma of the ovary.[3–5] A role for environmental factors and socioeconomical conditions in the origin of ovarian carcinoma has been inferred from its higher incidence in industrialized countries[6] (Table 2). The incidence of carcinoma of the ovaries in South African whites is substantially higher than in South African blacks.[5]

The products of industry upon which most attention has been focused are asbestos and talc. Whereas the carcinogenic properties of asbestos are undisputed,[7] there is still controversy over talc.[8] Although conclusive data are lacking, various facts indicate that talc could be a possible carcinogen, cocarcinogen, or promoter of malignant transformation, and should not be used as a dusting powder.[9] This is based on the fact that talc, a hydrous magnesium silicate [$Mg_6S_{18}O_{20}(OH)_4$] is chemically similar to asbestos, which is a calcium magnesium silicate [$Ca_2MG_5S_{18}O_{22}(OH)_2$]; besides, talc frequently contains microscopic fibers of asbestos as a contaminant.[10]

Access of talc to the peritoneal cavity is most likely through the vagina. Studies of the transport of particles in the human female reproductive tract have shown that nonmotile inert carbon particles deposited in the vagina can be recovered 30–35 min later in the fallopian tubes.[11]

Electron micrographic slides of removed human ovaries have shown asbestos particles resting on them, and there is evidence that these

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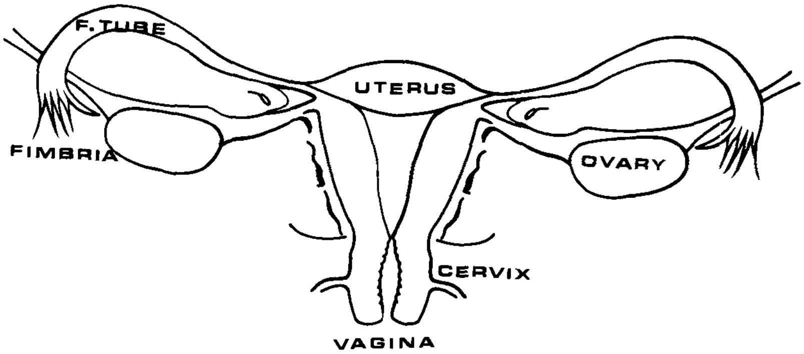


Fig. 1. Schematic representation of the female reproductive system pathways seen from in front.

particles originated from talc used to dust condoms.[12] In this circumstance, talc particles were probably thrusted by the penile pumping action during intercourse. Furthermore, Henderson et al. found talc particles deeply embedded in 75% of ovarian tumors studied.[13,14]

The potential harmful effects of talc on a highly differentiated tissue such as the ovary, with its interrelated cell types and cyclical changes of secretory activity, should certainly not be ignored.[15]

To demonstrate the upward migration of nonmotile, inert chemical substances we made use of radionuclide imaging and counting techniques.[16] During the course of the study, we came to recognize that the value of the images obtained outlining the female reproductive system pathways functionally reflected the dynamic state of this system and could be used as an additional and/or alternative diagnostic modality in clinical gynecologic practice in evaluating tubal patency. Diagnostic procedures where gases, fluids, dyes, and contrast medium are introduced through manual interventions under positive pressure from the uterine cervix into the peritoneum, are anatomically accurate and safe in the hands of those performing them regularly, but do not physiologically portray

Table 1. Possible Chemical Carcinogens Used in the Vagina for Cosmetic, Hygienic, and Medicinal Purposes*

1	Arsenicals
2	Hydroxiquinolines
3	Nitrofurantion
4	Ichthammol
5	Sulphonamides
6	Metronidazole
7	Nitrosamine†
8	Spermicides
9	Asbestos‡
10	Talc
11	Gentian violet

*From Venter.[5]
†Possible formation by chemical reduction.
‡As a contaminant.

Table 2. Incidence of Carcinoma of the Ovaries in Different Countries (per 100,000)*

Sweden	21.0
Norway	16.5
USA (whites)	15.6
England	14.7
Israel	11.0
USA (blacks)	8.8
USA (hispanics)	5.9
Africa	4.6
India	3.2
Japan	3.1

*From Kolstad and Beecham.[6]

Table 3. Surgical Indication and Operative Procedure (Group I)—24 Patients

No. Patients	Surgical Indication	Operative Procedure
4	Sterilization	Fimbriectomy
7	Ca. breast stage III	Bilateral salpingo-oophorectomy
1	Ca. breast stage III	Hysterectomy and bilateral salpingo-oophorectomy
2	Postmenopausal bleeding	Dilatation and curettage
2	Postmenopausal bleeding	Hysterectomy and bilateral salpingo-oophorectomy
3	Menorrhagia	Dilatation and curettage
4	Menorrhagia	Hysterectomy and bilateral salpingo-oophorectomy
1	Pelvic infection	Hysterectomy and bilateral salpingo-oophorectomy

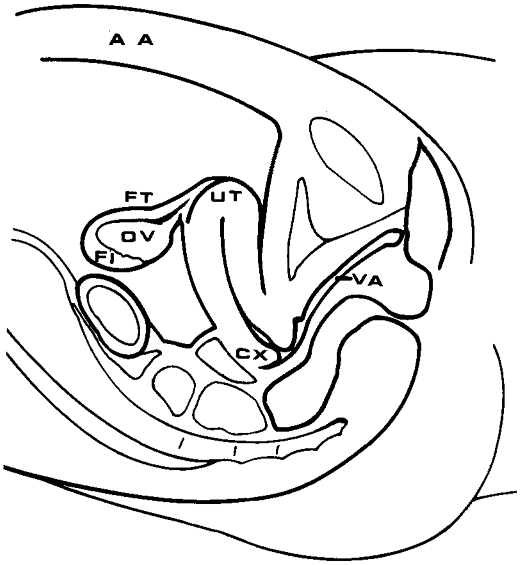


Fig. 2. **Median sagittal section of female genitalia to show relationships in the position in which the study was carried out. AA, anterior abdominal wall; VA, vagina; CX, cervix; UT, uterus; FT, fallopian tube; FI, fimbria; OV, ovary.**

fallopian tube patency. They are invasive procedures, uncomfortable for the patient, restricted under certain conditions, and not free of risks of hypersensitivity reactions inherent in any contrast medium.

MATERIALS AND METHODS

Patients in this study were divided into two different groups. Group I consisted of 24 adult women, both blacks and whites, admitted to hospital for elective gynecologic operations (Table 3). Group II consisted of 29 young white adult women referred by the Infertility Clinic for evaluation of their tubal patency. The radionuclide procedure was explained and the necessary consent was obtained.

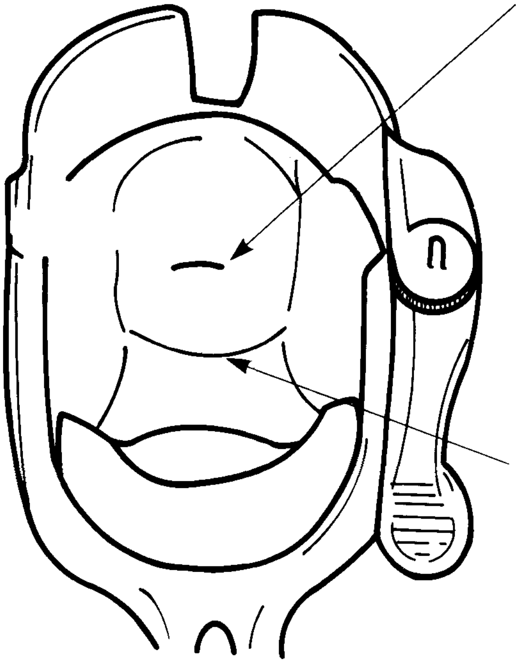


Fig. 4. **Exposed cervix seen from in front with arrows showing external cervical os and posterior fornix where ^{99m}Tc-HAM is usually deposited during HERS.**

Procedure

The patient was placed in the supine gynecologic examination position with the buttocks slightly elevated or in the Tredelenburg position. (Fig. 2). The cervix and posterior fornix were exposed with a Cusco vaginal speculum (Fig. 3) and 10 mCi (for patients of group I) and 2–3 mCi (for

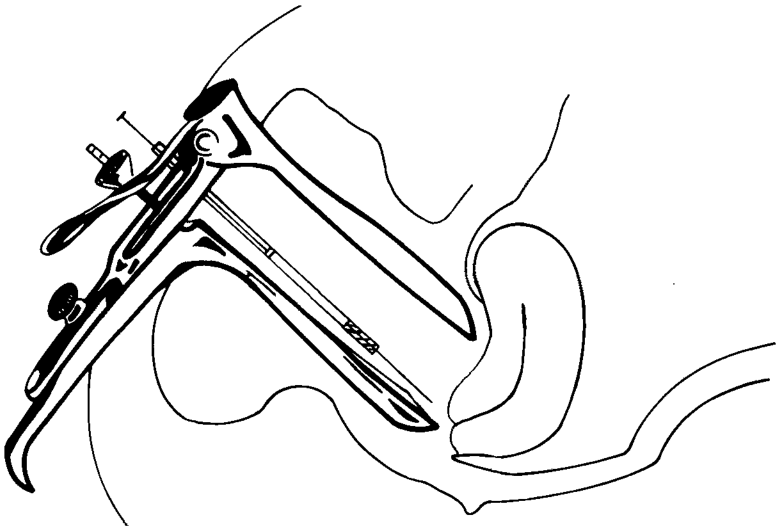


Fig. 3. **Cervix exposed with a Cusco vaginal speculum and syringe in place for deposition of ^{99m}Tc-HAM for HERS.**

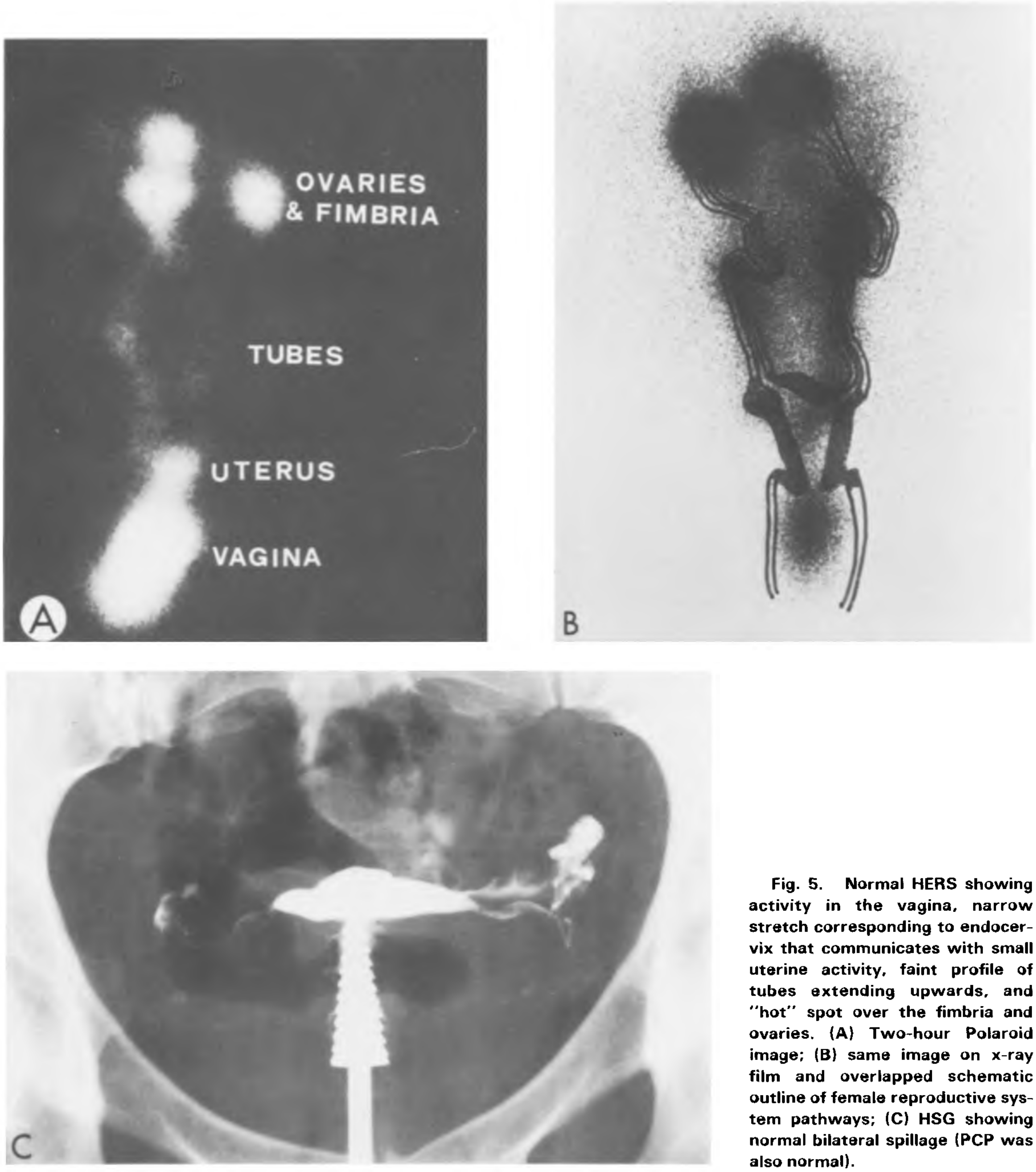
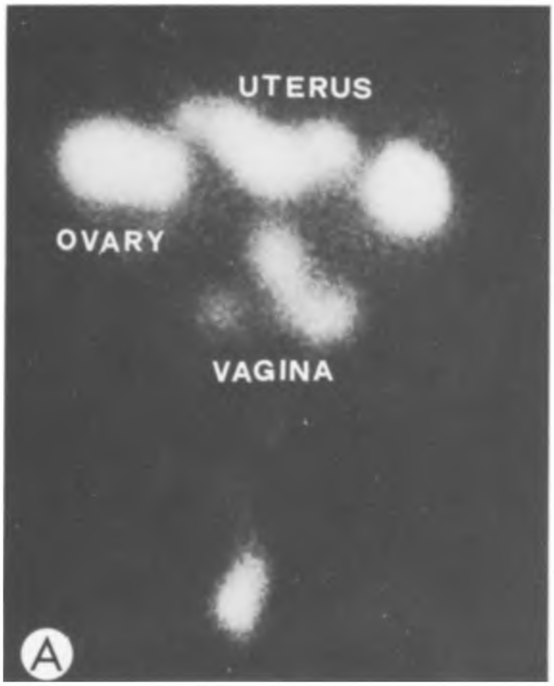


Fig. 5. Normal HERS showing activity in the vagina, narrow stretch corresponding to endocervix that communicates with small uterine activity, faint profile of tubes extending upwards, and "hot" spot over the fimbria and ovaries. (A) Two-hour Polaroid image; (B) same image on x-ray film and overlapped schematic outline of female reproductive system pathways; (C) HSG showing normal bilateral spillage (PCP was also normal).

patients of group II) of ^{99m}Tc-HAM in a volume of less than 1 ml were deposited in the posterior fornix, or close to the cervical external os (Fig. 4). The plastic cover of the needle (37 mm) was kept in place so as not to accidentally hurt the exposed tissue. The radionuclide was quickly discharged and the vaginal speculum carefully withdrawn while trying not to let the radioactive fluid leak out from the vagina. The vulva was then covered with a sanitary towel and the legs pressed or crossed together. The patient was kept in this position for the next 3 hr.

In patients from group I, about 24 hr after deposition of the radioactive tracer in the vagina, counts were performed on removed surgical specimens using a 12.7 cm well-scintillation detector. Where the uterus and adnexae were removed together, they were first counted as a whole and later separately. In the five patients that had D & Cs, only the endometrial scrapping was counted. In the case of fallopian tubes, each one was counted separately and the fimbria and ovaries separately from the isthmus. In two cases, a piece of the anterior peritoneum, fluid from the pouch of Douglas, peripheral blood, and lymphatic glands were also counted to determine the possibility of reabsorption of the radionuclide



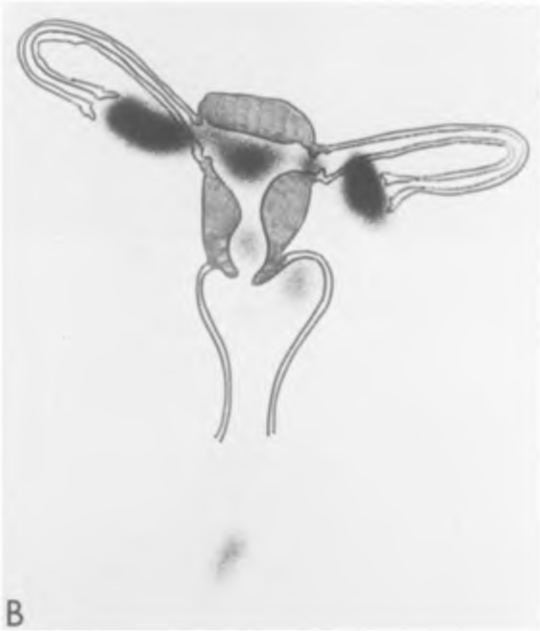


Fig. 6. Normal HERS; bicornate uterus with tubes extending laterally. (A) Three-hour Polaroid image; (B) same image with overlapped schematic outline of female reproductive system; (C) normal free spillage on HSG (PCP reported patent tubes).

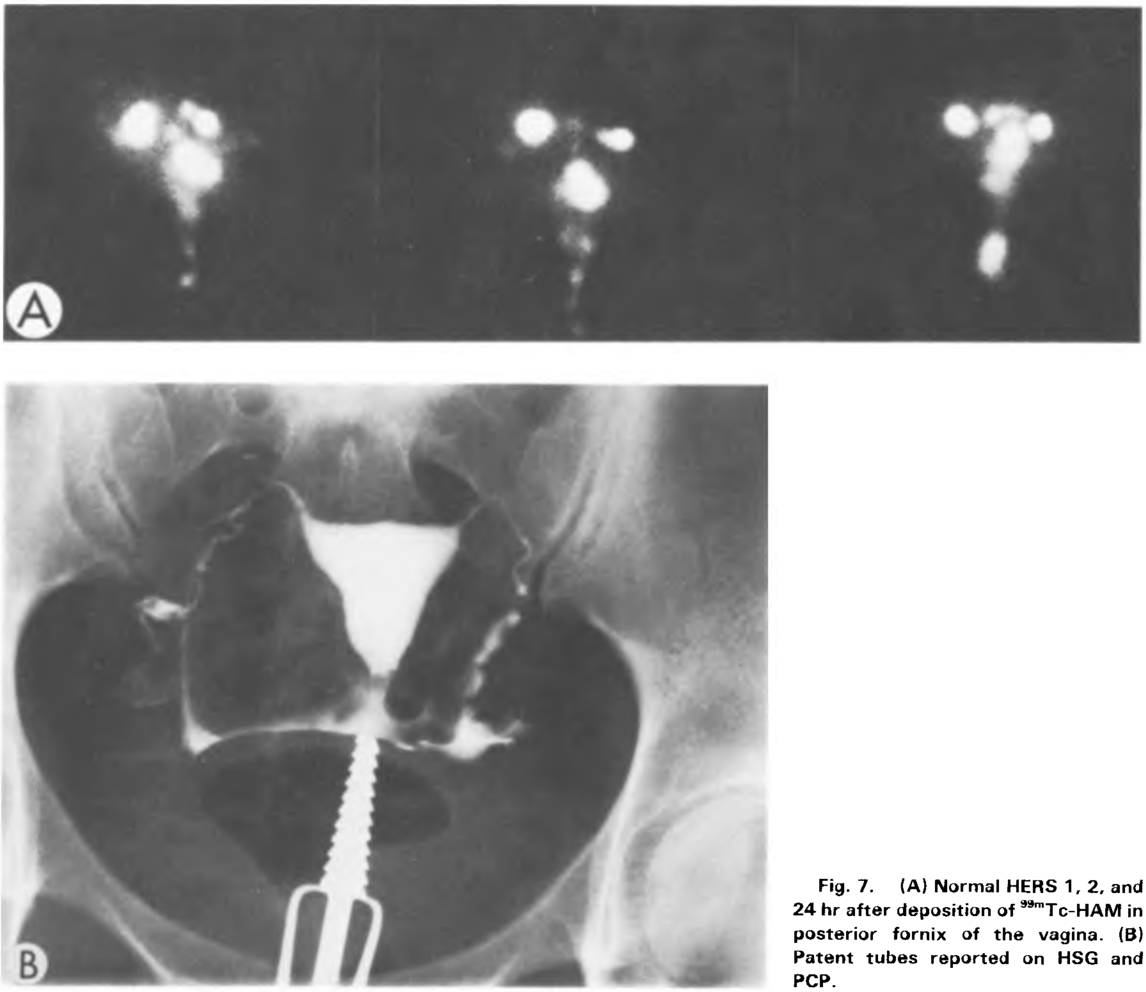


Fig. 7. (A) Normal HERS 1, 2, and 24 hr after deposition of ^{99m}Tc-HAM in posterior fornix of the vagina. (B) Patent tubes reported on HSG and PCP.

into the blood stream or lymphatic drainage from the vaginal mucosa.

If radioactivity levels measured on the removed surgical specimens were substantially higher than background levels, this constituted positive evidence of migration of the ^{99m}Tc-HAM from the vagina to the uterus or the tubes and ovaries. However, if radioactivity levels measured were comparable to background levels, it was taken as evidence that no migration of ^{99m}Tc-HAM had taken place and the cause for this possible obstruction was investigated.

Images were obtained 1, 2, 3, and 24 hr after deposition of the radioactive tracer on a large field of view gamma camera with a low-energy parallel all-purpose collimator, to a total of 400–500 K counts. The usual was an anterior view over the lower pelvic region, and in selected cases, images were also obtained shielding the high activity in the vagina in order to enhance the image of the uterus and tubes. Scintiphotos were recorded on Polaroid and x-ray film.

The normal pattern of the images obtained with this procedure would be a central elongated area of high activity over the vagina. Directly on top of this area would be a narrow stretch of activity corresponding to the endocervix, which would communicate the vagina and intrauterine activity. The uterus appeared as a smaller area of varying size, position, and shape (in most cases it was triangular). The tubes would be seen extending laterally or upward in a diverging angle with a distal "hot" spot of high intensity corresponding to the fimbria and ovaries (Fig. 5). In some cases, activity in the region of the tubal isthmus could not be visualized, although there was high activity in their distal segment (Figs. 6 and 7). In most cases, activity progressed within the first hour simultaneously through both tubes, while in others, activity moved faster in one tube than in the other, showing increased activity on one side. (Fig. 8). Scans were interpreted as abnormal if there was no activity in one or both tubes and specially if the distal focal area of high activity in the fimbria did not show up (Figs. 9, 10, and 11). Anatomic variants were also detectable (Fig. 12).

All patients of group II also had contrast hysterosalpingography (HSG) and peritoneoscopy (PCP) done after HERS. Spillage of the contrast media into the peritoneal cavity during HSG or appearance of the dye in the fimbria during PCP was an evident sign of tubal patency. The pressure exerted to introduce these substances from the

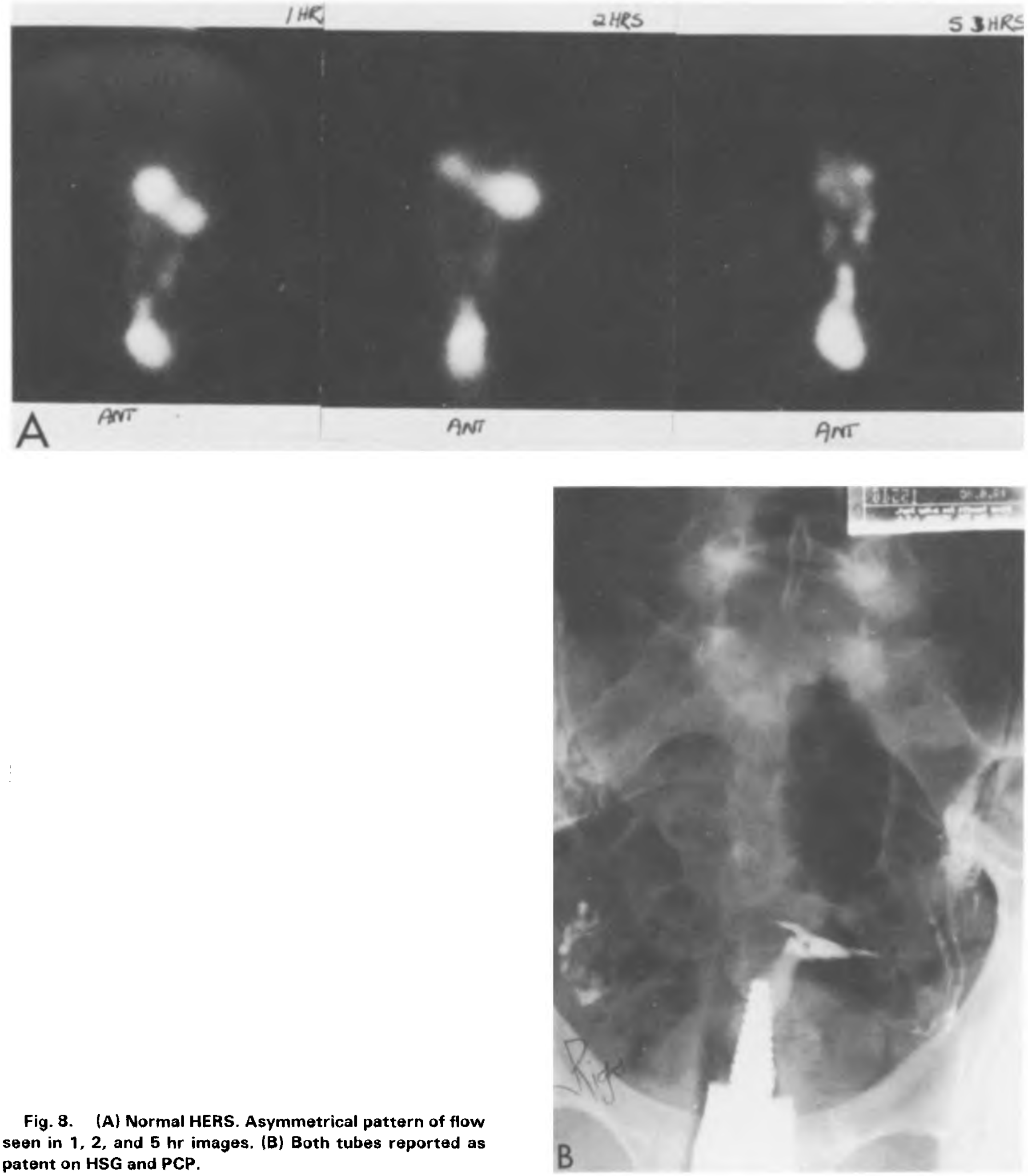


Fig. 8. (A) Normal HERS. Asymmetrical pattern of flow seen in 1, 2, and 5 hr images. (B) Both tubes reported as patent on HSG and PCP.

uterine cervix to the peritoneal cavity was also taken into consideration. Results of the three diagnostic procedures were later compared and clinically evaluated. (See Results below.)

Radiation exposure to patients of group I was low or in most cases negligible, since the target organs had been surgically removed. However, this was not the case for patients of group II who were sexually active and in potentially childbearing age.

We were concerned because the radioactivity reaching the fimbria and ovaries, which in this case were the target organs, decayed there physically, as there is no know mechanism for the biologic removal of the ^{99m}Tc-HAM once they reach the critically radiosensitive gonads. For this reason, we reduced the dose of the deposited ^{99m}Tc-HAM in the vagina to 2–3 mCi during the course of the study of patients from group II without sacrificing clinically informative value to the procedure.

Fortunately, most of the deposited radioactivity appears to be in the vagina and only a fraction of it migrates to the

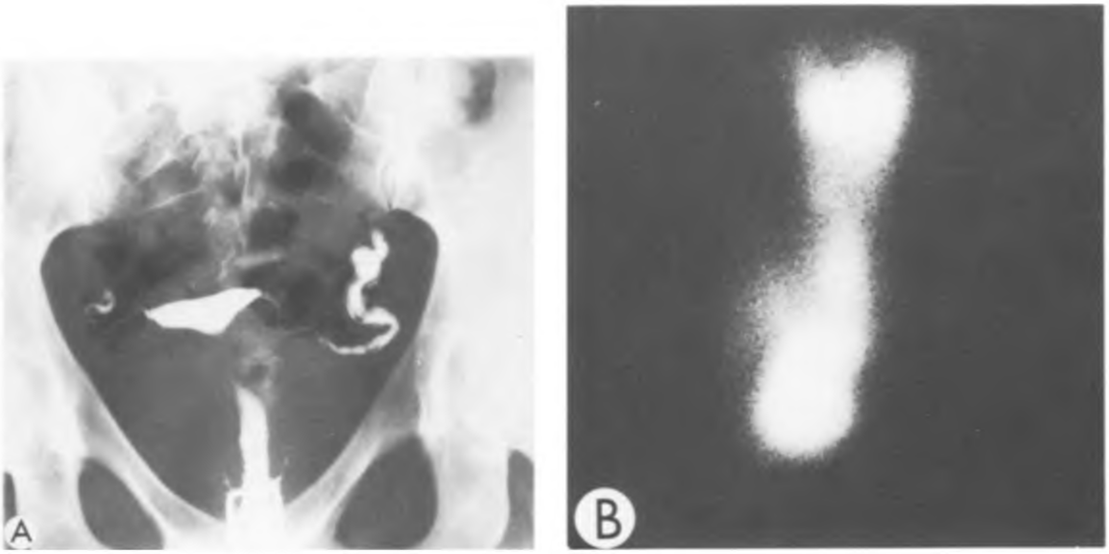
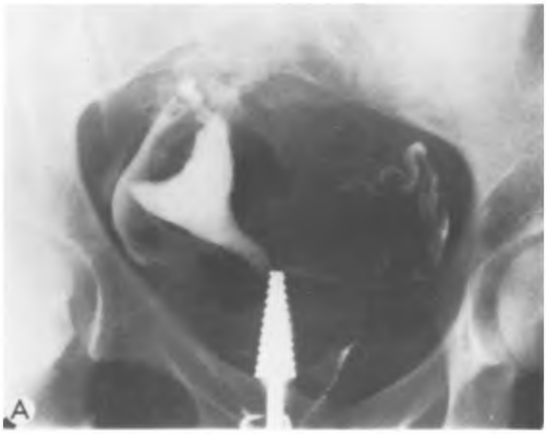


Fig. 9. Patient with left side hydrosalpinx. (A) HSG shows a dilated and contorted left tube with a short and thin right tube. There was spillage in the left side with obstruction in the right side tube. (B) A 2-hr image of HERS shows the same pattern with no migration of ^{99m}Tc-HAM in the right tube.

uterus and tubes (Fig. 13). Furthermore, in most cases this migration occurs within the first 3 hr and no further imaging is needed at 24 hr, which makes it possible to still obtain good quality images while reducing the radiation dose to the patient to safer levels comparable to those of x-ray diagnostic procedures.[17]

RESULTS

Because the radioactive material leaked out from the vagina in 3 patients, these patients were excluded from the final analysis of the 24 patients of group I (Table 4). In 16 of the



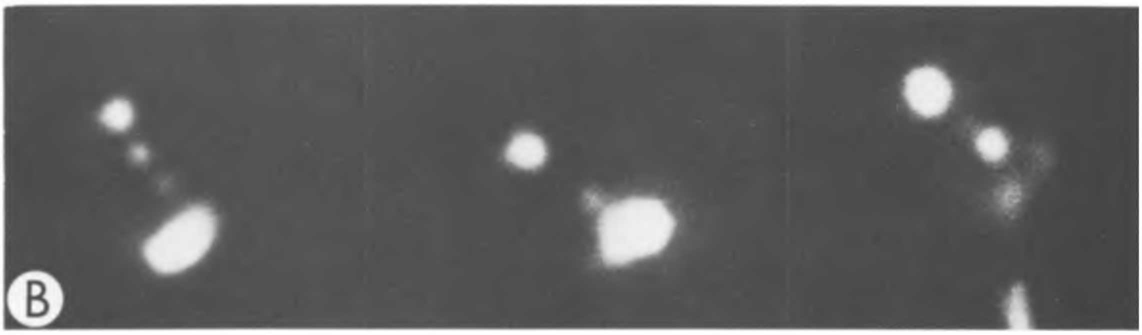


Fig. 10. HERS and HSG (A) show uterus displaced to the right with long contorted left tube and obstructed right tube. (B) HERS on the 2, 3, and 24 hr images show focal "droplets" of higher activity at site of prominent kinks of left tube.

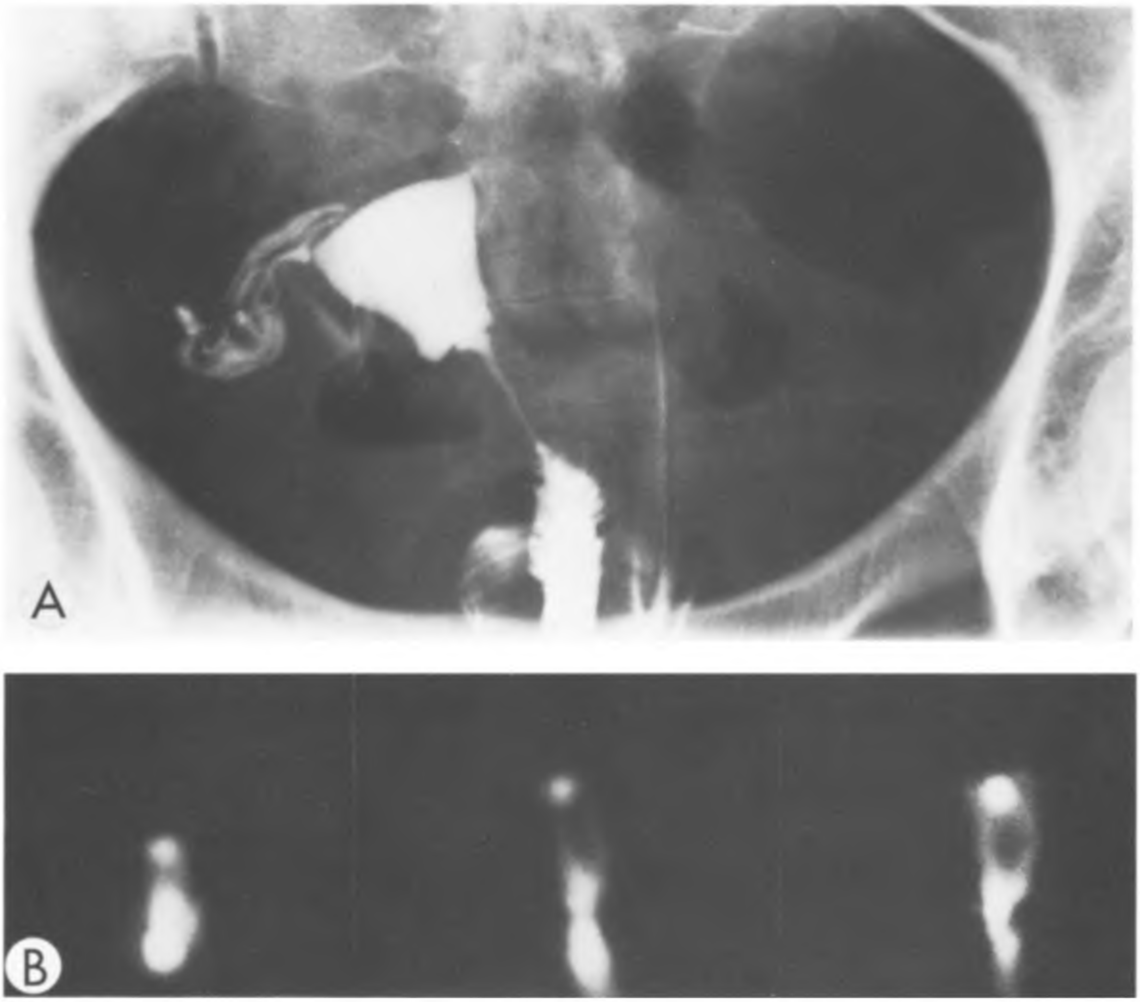


Fig. 11. (A) HSG shows right tube to be patent while the left tube is only seen in its proximal segment. (B) HERS shows the same pattern at 1 and 2 hr. Later, at 24 hr, activity can be seen migrating through left tube but not reaching the fimbria.

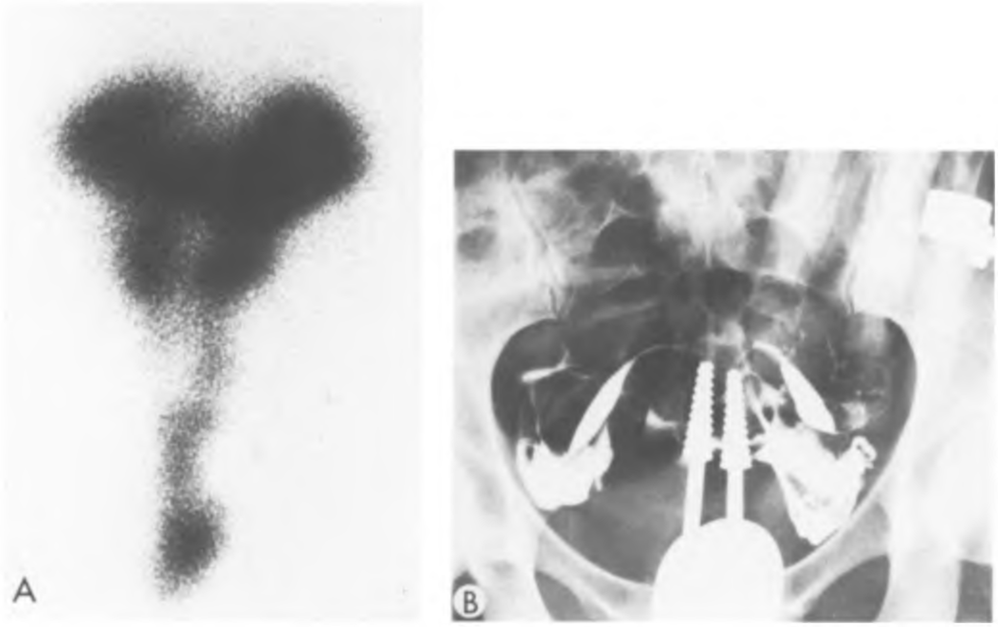


Fig. 12. Patient with didelphos as outlined on 1-hr image of HERS (A) and HSG (B).

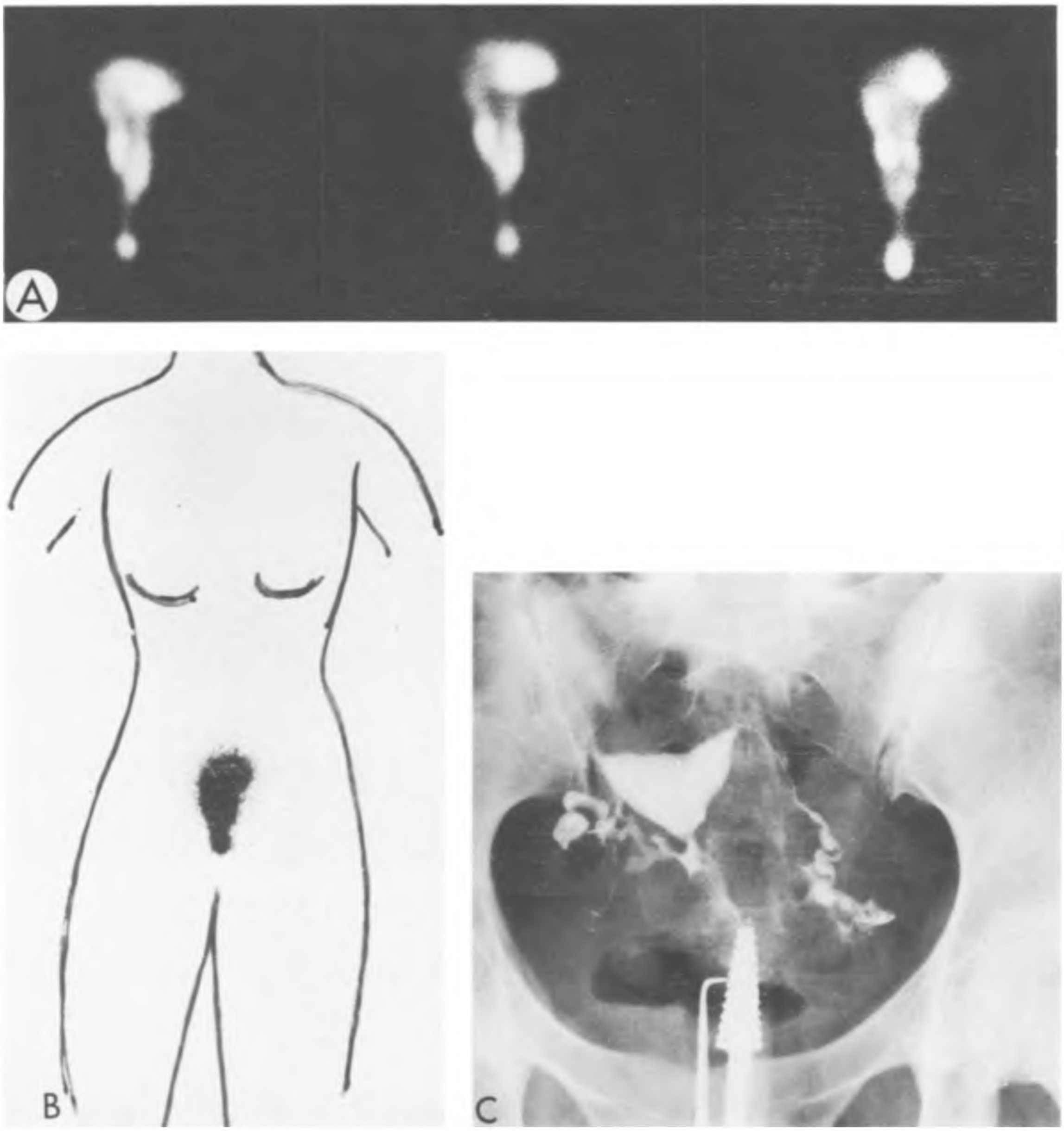


Fig. 13. **(A) HERS shows a normal pattern of migration on 2, 3, and 24-hr images. (B) Twenty-four-hour whole body scan shows activity exclusively in the area of interest. (C) Bilateral tubal patency reported on HSG and PCP.**

Table 4. Summary of Results (Group I)

Positive migration	16
Negative migration	
No passage to uterus	2
No passage to adnexae	3
Technically defective	3
Total patients examined	24

Table 5. HERS Versus HSG and PCP (Group II)

Agreement between HERS, HSG, and PCP	21
Disagreement between HERS/HSG and PCP	
HERS (−); HSG and PCP (+)*	5
HERS (+); HSG and PCP (−)	1
Technically defective	2
Total patients examined	29

*Tubes patent (+); tubes not patent (−).

remaining 21 patients there was positive evidence of migration of the ^{99m}Tc-HAM from the vagina to the uterus or the tubes and ovaries. The results were negative in 5 cases; in 2 of them the radioactive ^{99m}Tc did not pass from the vagina to the uterus, and in the other 3 there was no migration to the adnexae or fimbria.

In 14 of 21 cases, it was possible to measure high radioactivity levels in the adnexae separately from the uterus. Nine of these showed marked radioactivity in the tubes and ovaries (most of it localized in the fimbria). In 5 cases, radioactivity levels in the tubes were not much higher than the background, and in these patients severe tubal occlusion due to previous infection was confirmed by pathologic study of the surgically removed specimens. In the two patients where pieces of the anterior peritoneum, peripheral blood, and lymphatic glands were counted, the radioactivity levels of the samples were as low as that of the background. This showed that the ^{99m}Tc-HAM had not reached the adnexae through the blood supply owing to local reabsorption or lymphatic drainage from the vaginal mucosa where they had been deposited.

When HERS was compared with the results of HSG and PCP in group II (Table 5), we found that in 21 patients there was complete accordance between the 3 diagnostic modalities, be it that the tubes were patent or occluded. In one case, HSG and PCP showed that the tubes were patent, while initially HERS showed no migration in one tube during the first 3 hr of observation, but this changed later at 24 hr, when radioactivity appeared in the distal end of that tube (Fig. 14). In 6 cases there was no agreement between HERS and HSG and PCP. In 5 of them, both HSG and PCP showed that the tubes were patent when the contrast media and the dye were introduced under extreme pressure (Figs.

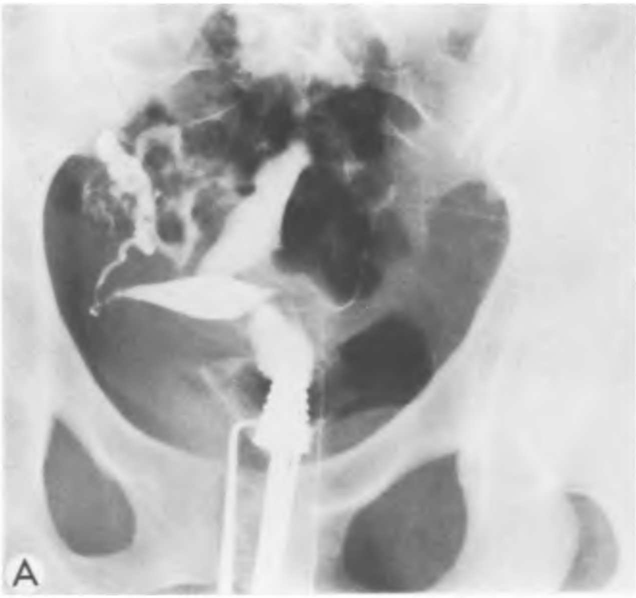


Fig. 14. **(A) HSG shows bilateral tubal patency. (B) Two hour and 3 hr images on HERS show migration on left tube only, which appears to be long and contorted. At 24 hr, radioactivity appears to have migrated through right tube as well.**

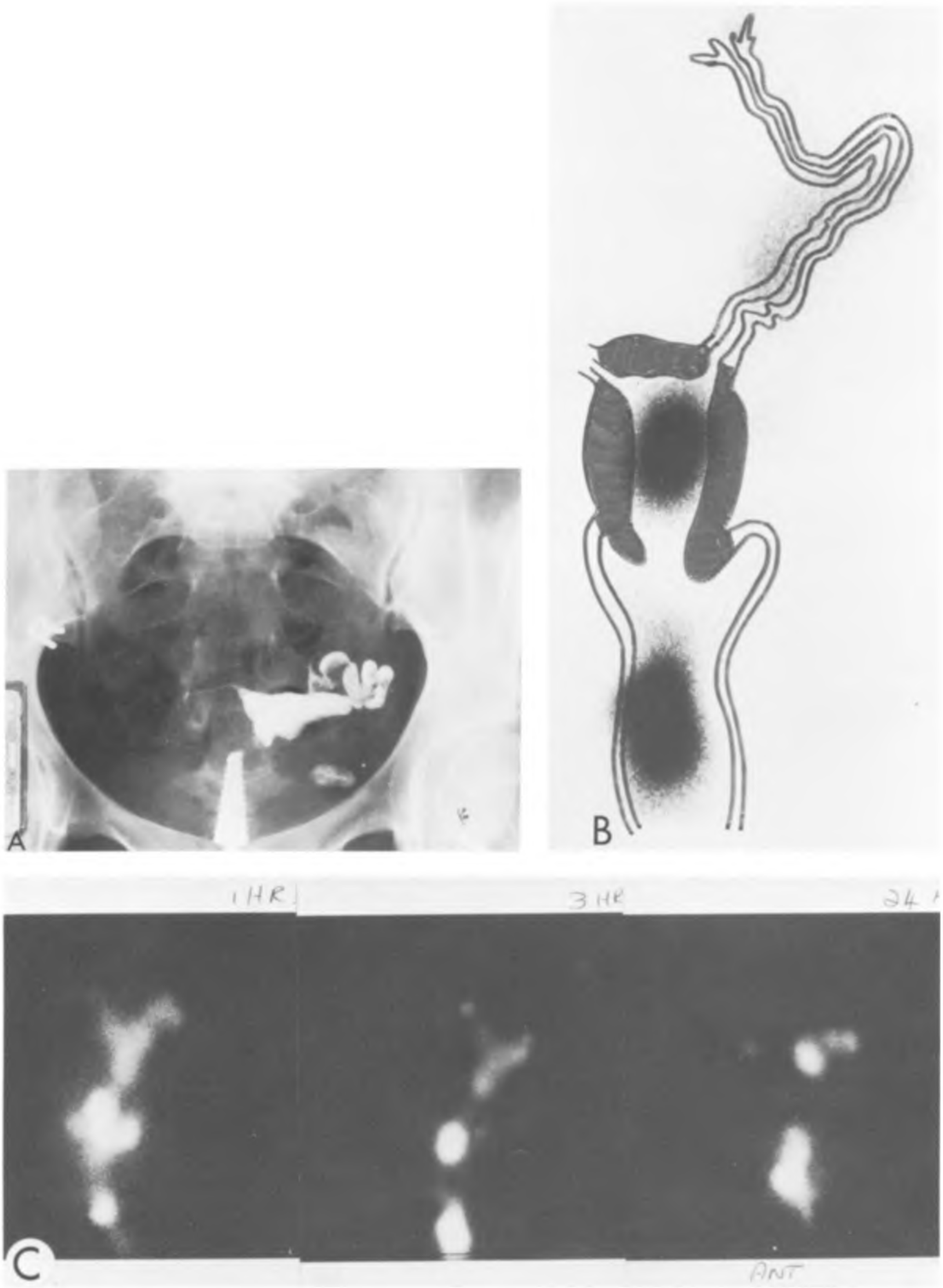


Fig. 15. (A) During HSG and PCP both tubes were reported to be patent, but only after introducing contrast media and dye, respectively, under extreme pressure. (B and C) HERS shows that up to 24 hr, there is no migration through the right tube, while the left tube appears long and kinked.

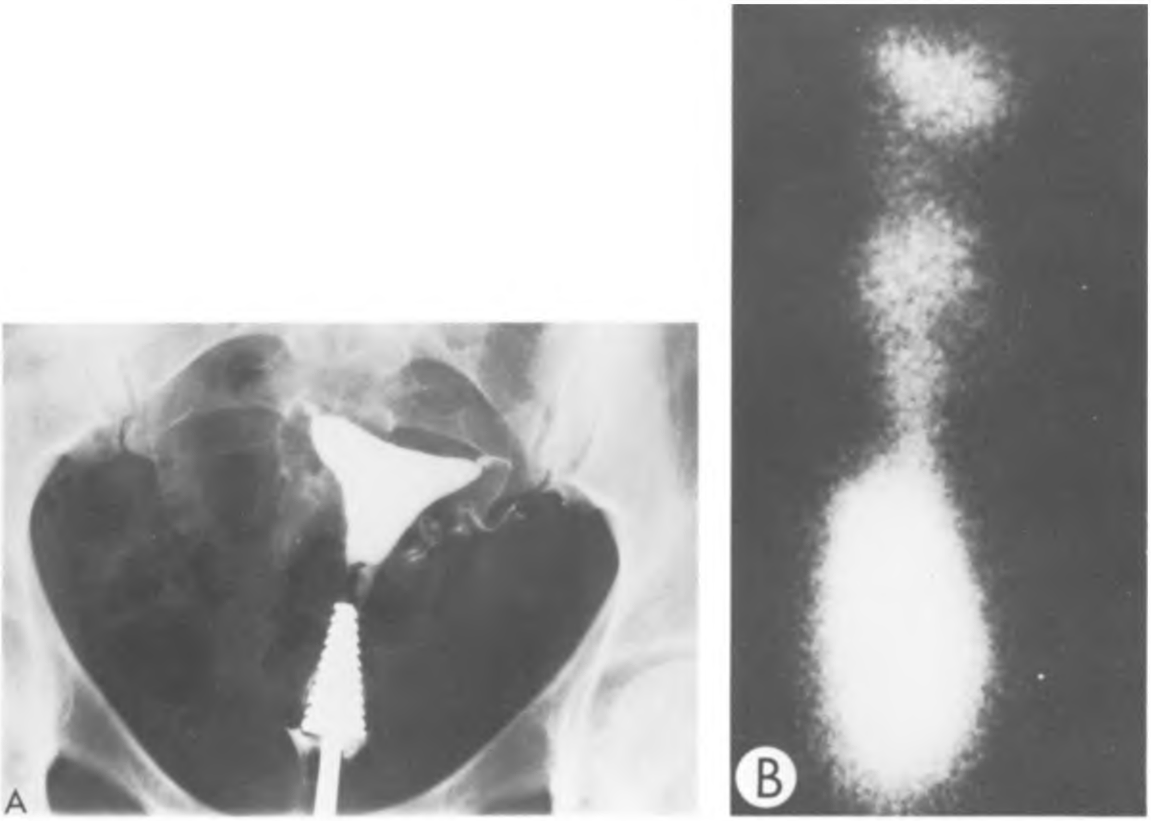


Fig. 16. (A) During HSG and PCP, both tubes were reported to be patent, but only after introducing contrast media and dye, respectively, under extreme pressure. (B) On the 24-hr image, HERS shows no migration of ^{99m}Tc-HAM through the right tube.

15 and 16). In these 5 cases, HERS showed no evidence of migration in one or the other tube, reflecting in this way the physiologic state of the fallopian tubes. In only one case did HERS show patency in one tube, while HSG and PCP did not, this was in the case of a woman with a septum in her vagina and a double uterus where manipulations for HSG and PCP were difficult. Finally, in 2 cases the results were equivocal because at least 2 of the 3 diagnostic procedures were technically deficient and no clinical information of diagnostic value could be obtained.

DISCUSSION

The results obtained from HERS in patients from group I clearly demonstrate the upward migration of a particulate radioactive tracer such as ^{99m}Tc-HAM from the vagina through the uterus and tubes into the peritoneal cavity and ovaries. This evidence correlates with findings on the surgically removed specimens, proving the accuracy of this radionuclide procedure. The real importance of this finding is that it supports previous evidence for the migration of inert, nonmotile chemical substances from the vagina to the peritoneum and ovaries,[11–14] and could help explain the role that some of these apparently innocent and frequently used substances play in the etiology of certain gynecologic diseases.[3,4,8,9]

The mechanism by which this migration takes place is not clearly defined, but it is assumed that it is a combination of muscular peristaltic movements, changes in peritoneal pressure, and ciliary motion (in the tubes) that drives particles from the vagina to the peritoneum and ovaries. The abundance of blood vessels interspersed with muscle bundles and active mucosal secretion form in the fimbria a kind of erectile tissue where most of the tubal activity tends to gravitate. There must also be a cyclical hormonal component regulating this process, and we

presume that migration is facilitated during the period of ovulation.

As far as the radionuclide imaging process is concerned, it was encouraging to find a close correlation of this procedure when compared with HSG and PCP. But most important of all is the fact that HERS functionally reflects the dynamic state of the female reproductive system pathways by showing particulate migration, which is not the case of the other anatomically dependant diagnostic modalities used to evaluate tubal patency. In this small series we found that in five cases, HSG and PCP were reported showing anatomical tubal patency only because both the contrast media and dye were injected under extreme pressures, opening tubes that under other circumstances would not be patent. HERS proved in these five patients (19% of the series) that there was no migration of ^{99m}Tc-HAM through the fallopian tubes, this being the probable cause for the infertility of these patients.

Even though HERS is a simple, safe, and accurate procedure, further studies will be necessary to establish its value as an additional and/or alternative study to other conventional procedures in evaluating tubal patency and its role as a functional radionuclide imaging modality in clinical gynecologic practice.

One indication for HERS would be to use it as a procedure to monitor the efficacy of sterilization procedures where the fallopian tubes are dissected or obstructed; or conversely to see if they are patent and open to transit after reconstructive surgery in patients that have been previously sterilized. In both cases the patient becomes her own control before and after the surgical procedure.

REFERENCES

1. Greenfeld EF: Ovarian tumours. Clin Obstet Gynecol 18:61–86, 1975
2. Schwarz RH: Acute pelvic inflammation disease, in Monif GRG (ed): Diseases in Obstetrics and Gynaecology. London, Harper and Row, 1974, pp 381–395
3. Howe JR: A method of recognising carcinogens in the laboratory. Lab Prac 24:457–467, 1975
4. Lingeman CH: Etiology of cancer of the human ovary. A review. J Natl Cancer Inst 53:1603–1618, 1974
5. Venter PF: Epiteeltumore van die Ovarium. Doctoral thesis University of the Orange Free State, South Africa, 1979
6. Kolstad P, Beecham J: Epidemiology of ovarian neoplasia, in: Diagnosis and Treatment of Ovarian Neoplastic alterations. Amsterdam, Exerpta Medica, American Elsevier, 1975, pp 56–62
7. Wagner JC: Asbestos and cancer. Abbottempo Book 3:26–29, 1968
8. Henderson WJ, Hamilton TC, Griffiths K: Talc in normal and malignant ovarian tissue. Lancet 1:499, 1979
9. Longo DL, Young RC: Cosmetic talc and ovarian cancer. Lancet 2:349, 1979
10. Moorehead WR, Tjein OO: Talc in drugs. N Engl J Med 298:1365–1366, 1978
11. Egli GE, Newton M: The transport of carbon particles in the human female reproductive tract. Fertil Steril 12:151–155, 1961
12. Deutsch M: More on joggers ailments. N Engl J Med 298:405, 1978
13. Henderson WJ, Joslin CAF, Turnbull AC, et al: Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw 78:266–272, 1971
14. Henderson WJ, Melville-Jones C, Wilson DW, et al: Oxygen incineration and electron microscope x-ray microanalysis of mineral particles in biological tissue. J Histochem Cytochem 26:1087–1093, 1978
15. Griffiths K, Chandler SA, Henderson WJ, et al: Ovarian cancer: Some new analytical approaches in carcinoma of the ovary. Postgrad Med J 49:69–72, 1973
16. Venter PF, Iturralde M: Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. S Afr Med J 55:917–919, 1979
17. Johns HE, Cunningham JR: Patient exposure in diagnostic radiology, in Johns HE, Cunningham JR (eds): The Physics of Radiology. Springfield Ill, Charles C Thomas, 1969, pp 638–644

Exhibit 47

The Transport of Carbon Particles in the Human Female Reproductive Tract

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THE METHOD by which spermatozoa reach the oviduct remains an important problem in mammalian reproduction. Since spermatozoa possess motility, it has been widely assumed to be the most important factor. However, work in cows suggests that it may not be the chief means of transport. Thus, Vandemark and Moeller recovered spermatozoa from the oviduct 2½ min. after mating. This is far sooner than could be expected on the basis of the inherent motility and sense of direction of spermatozoa.

Work in animals indicates that muscular contractions of the reproductive tract may aid in the transport of spermatozoa and that the oxytocic hormone may play a part in this process. Vandemark and Hays[11] noted that a crescendo of uterine contractions took place before and during copulation in the cow. Furthermore, stimulation of the cow's genitalia produced a rise in intramammary pressure.[7] Normally such a change is brought about by the release of oxytocin from the posterior pituitary gland during the letdown or ejection reflex as the calf or milking machine is applied to the teat.[5] Finally, in-vitro studies by Vandemark and Hays[12] demonstrated that when oxytocin was added to the solution perfusing the isolated cow's uterus, the rate of transport of spermatozoa was increased.

Evidence that the same process occurs in humans is scanty. Because of the difficulty of using spermatozoa, inert particles have occasionally been employed experimentally. Amersbach placed a cap containing a suspension of carbon particles over the cervix. Following coitus he was able to recover

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particles from the cervical canal. Trapl had a patient insert carmine particles into the vagina immediately after intercourse. Twenty-four hr. later at laparotomy he found numerous particles in the uterine tubes. Furthermore, it has been suggested that there may be a sucking effect as a result of uterine contractions occurring at orgasm that pulls semen through the cervix into the uterus.[8] There is also some evidence that oxytocin is released at the time of orgasm in humans.[4, 9] However, the time relationships and precise mechanisms of transport of inert particles or spermatozoa have not been elucidated in humans. The paucity of information in this regard has been pointed out by Hartman in his excellent review article.

If human spermatozoa move at a rate of 3 mm./min.,[3] it should take a spermatozoon, moving on a direct course, at least 45 min., in the average woman, to travel from the cervix to the junction of the middle and outer thirds of the tube, where fertilization occurs. If the action of the uterine or other muscles of the reproductive tract is important in humans, then not only spermatozoa but also inert particles should reach the tube much sooner than this. The present study was designed to determine whether, under reasonably controlled conditions, carbon particles could be transported quickly from the vagina to the tubes.

METHODS

It seemed desirable to set up, as far as possible, conditions that were optimal for rapid transport. Thus, patients were selected who required an elective abdominal hysterectomy that could be scheduled at or near the day of ovulation. They had to be of reproductive age, to have proved fertility, and to have relatively normal reproductive organs. A suspension of carbon particles in Dextran was made up so that the particles were similar in size to spermatozoa and that the solution was of the consistency of seminal fluid. This was done by mixing 30% Dextran with 4% bone black. In addition, it was decided to use intramuscular oxytocin to aid in the transport of the particles, because of the experimental evidence indicating its possible importance.

Three women fulfilling the above criteria were studied. In each instance the procedure was as follows: Soon after general anesthesia had been induced, the patient was placed in the lithotomy position with her head tilted downward at an angle of 15° from the horizontal. A speculum was introduced into the vagina, and 3–4 ml. of sterile carbon particles–Dextran suspension were deposited in the posterior fornix. At the same time 1 ml.

(10 U.) of oxytocin was given intramuscularly. The speculum was removed, and the patient was immediately returned to the supine flat position. Her abdomen was promptly opened, and before the uterus was manipulated, a suture was placed tightly around the tubes about 1 cm. lateral to the uterus. The tubes were excised and taken to the laboratory, where they were flushed with saline from the infundibular portion downward. The solution was collected on clean slides and examined under the microscope for carbon particles.

RESULTS

The first patient was 32 yr. of age, gravida 6, para 6, and was at the fourteenth day of her cycle, which was usually about 28 days in length. Twenty-eight min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Many carbon particles were found in the washings from both tubes. On microscopic examination the endometrium was described as being early progestational.

The second patient was 30 yr. of age, gravida 6, para 6, and was at the twelfth day of her cycle, which was usually about 28 days in length. Thirty-four min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. Carbon particles were recovered from both tubes. On microscopic examination the endometrium was described as being estrogenic.

The third patient was 41 yr. of age, gravida 8, para 7, aborta 1, and was at the thirteenth day of her cycle, which was usually about 28 days in length. She was a diabetic and had aborted three mo. previously. Twenty min. after the carbon-particle suspension had been deposited in the posterior fornix, the tubes were ligated and then excised. No carbon particles were found in the washings from either tube. On microscopic examination the endometrium was described as being early progestational.

DISCUSSION

This study indicates that in two cases, under the conditions outlined, inert carbon particles, placed in the posterior fornix of the vagina, were found 28 and 34 min. later in both tubes. How they reached the tubes is a difficult question to answer. Certainly they did not proceed by their own movements. It is reasonable to suppose that some sort of movement of the uterus and/or tubes contributed to the transport of the particles.

Movements of the reproductive organs and particularly the uterus could be due to inherent motility, general body movements, the effect of anes-

thesia, or the influence of the injected oxytocin. The uterus undoubtedly possesses inherent motility. Conceivably this could be sufficient to aid the transport of particles into the tubes, although it might well have been decreased by the anesthesia used. Bodily movements were held to a minimum. The patients were on their backs at all times, and so virtually no opportunity for the suspension to enter the uterus or tubes by gravity was afforded. Manipulation consisted only of removing the speculum, returning the patient to the supine position, opening the abdomen, and ligating the tubes. The effect of anesthesia would be, in general, to reduce uterine motility: However, spasm of the cervix or uterotubal opening could have been relaxed by the anesthesia. The theory that oxytocin does contribute to the transport of particles is most attractive, but at the present time we have no proof of it. Further in-vivo and in-vitro experiments are being done in pursuit of a solution to this problem.

The fact that in one case transport of carbon particles to the tubes was not demonstrated is not surprising. One of several factors may have contributed to this. Possibly the hormonal conditions present in the uterus were not optimal.[2] The patient's recent abortion may have been important. Finally, it is conceivable that insufficient time was allowed for transport.

SUMMARY AND CONCLUSIONS

Carbon particles, suspended in 30% Dextran, were placed in the vagina in three anesthetized women who were about to undergo elective abdominal hysterectomy at about the time of ovulation. At the same time oxytocin was injected intramuscularly. In two of the three women carbon particles were recovered from the tubes 28 and 34 min. later.

These data, together with other work in animals and humans, support the belief that the motility of spermatozoa is not the chief factor in sperm transport. Contractions of the muscle of the uterus or other reproductive organs may be very important, and it is possible that oxytocin may play a part in this process.

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REFERENCES

1. Amersbach, R. Sterility and frigidity. *München. med. Wchnschr. 77*:225, 1930.
2. Bickers, W. Sperm migration and uterine contractions. *Fertil. & Steril. 11*:286, 1960.
3. Brown, R. L. Rate of transport of spermia in human uterus and tubes. *Am. J. Obst. & Gynec. 47*:407, 1944.

4. Campbell, B., and Petersen, W. E. Milk "let-down" and the orgasm in the human female. *Human Biol.* *25*:165, 1954.
5. Ely, F., and Petersen, W. E. Factors involved in the ejection of milk. *J. Dairy Sc.* *24*:211, 1941.
6. Hartman, C. G. How do sperms get into the uterus? *Fertil. & Steril.* *8*:403, 1957.
7. Hays, R. L., and Vandemark, N. L. Effect of stimulation of the reproductive organs of the cow on the release of an oxytocin-like substance. *Endocrinology* *52*:634, 1953.
8. Kinsey, A. C., Pomeroy, W. B., Martin, C. E., and Gebhard, P. H. *Sexual Behavior in the Human Female.* Philadelphia, Saunders, 1953, p. 633.
9. Pickles, V. R. Blood flow estimations as indices of mammary activity. *J. Obst. & Gynaec. Brit. Emp.* *60*:301, 1953.
10. Trapl, J. New views on the transport of ova and sperm in the female reproductive tract. *Zentralbl. Gynäk.* *67*:547, 1943.
11. Vandemark, N. L., and Hays, R. L. Uterine motility responses to mating. *Am. J. Physiol.* *170*:518, 1952.
12. Vandemark, N. L., and Hays, R. L. Sperm transport in the perfused genital tract of the cow. *Am. J. Physiol.* *183*:510, 1955.
13. Vandemark, N. L., and Moeller, A. N. Speed of spermatozoan transport in reproductive tract of estrous cow. *Am. J. Physiol.* *165*:674, 1951.

Exhibit 48

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Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

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Abstract

Background: Epidemiologic studies indicate increased ovarian cancer risk among women who use genital powder, but this has not been thoroughly investigated in African American (AA) women, a group with a high prevalence of use. We evaluate the relationship between use of genital powder and nongenital powder in invasive epithelial ovarian cancer (EOC).

Methods: Subjects are 584 cases and 745 controls enrolled in the African American Cancer Epidemiology Study (AACES), an ongoing, population-based case–control study of EOC in AA women in 11 geographic locations in the United States. AA controls were frequency matched to cases on residence and age. Logistic regression was used to calculate ORs and 95% confidence intervals (CI) for associations between genital and nongenital powder exposure and EOC risk, controlling for potential confounders.

Results: Powder use was common (62.8% of cases and 52.9% of controls). Genital powder was associated with an increased risk of EOC (OR = 1.44; 95% CI, 1.11–1.86) and a dose–response relationship was found for duration of use and number of lifetime applications ($P < 0.05$). Nongenital use was also associated with EOC risk, particularly among nonserous EOC cases (OR = 2.28; 95% CI, 1.39–3.74). An association between powder use and upper respiratory conditions suggests an enhanced inflammatory response may explain the association between body powder and EOC.

Conclusions: In a study of AA women, body powder use was significantly associated with EOC risk.

Impact: The results support that body powder is a modifiable risk factor for EOC among AA women. *Cancer Epidemiol Biomarkers Prev; 25(10); 1411–7. ©2016 AACR.*

See related commentary by Trabert, p. 1369

Introduction

Genital powder use may be a modifiable risk factor for epithelial ovarian cancer (EOC), the most deadly of all gynecologic cancers (1). In 2010, the International Agency for Research on Cancer (IARC) classified perineal (genital) use of nonasbestos–containing, talc-based body powder as "possibly" carcinogenic to humans (2). Although particles of asbestos have been found in older body powder formulations, particularly prior to 1976 (3), more recent body powder formulations no longer contain asbestos (4, 5). However, the relationship between genital powder use and ovarian cancer appears to persist (6). It has been proposed that talc-containing powders may promote cancer development through local inflammation, increased rates of cell division and DNA repair, increased oxidative stress, and increased cytokine levels (7).

A recent pooled analysis of eight population-based case–control studies demonstrated an elevated OR of 1.24 for the association between genital powder use and EOC (6). Some (7–15) but not all (6, 8, 16) previously published studies of talc and ovarian cancer reported a dose–response relationship with genital powder use for frequency, duration, or number of applications. In addition, some studies reported a stronger association among the most common serous histologic subtype (4, 10, 14, 16, 17) although the pooled analysis did not confirm this finding (6). Only one prospective study (17) found a significant association with ever genital talc use and invasive serous EOC (RR = 1.40; 95% CI, 1.02–1.91), although no overall association with EOC was found. The Women's Health Initiative (WHI; ref. 18) did not detect an association with

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genital talc use and EOC. Neither prospective study found evidence of a dose–response relationship.

Previous studies of genital powder use have included mostly white women. However, two studies reported analyses stratified by race and both found an increased EOC risk among African American (AA) women who used genital talc (14, 15). One study reported a nonsignificant association between one or more years of talc use and risk of ovarian cancer, OR = 1.56, [95% confidence interval (CI), 0.80–3.04] among a small sample of 128 AA EOC cases and 143 AA controls, who were shown to have higher prevalence of talc use compared with whites (14). A second study reported an imprecise but significant association with genital talc use with an OR of 5.08 (95% CI, 1.32–19.6) among a very small sample of 16 cases and 17 controls (15). In this article, we present analyses of the relationship between both genital powder and nongenital powder exposure from the African American Cancer Epidemiology Study (AACES), an ongoing, multicenter case–control study of invasive EOC in AA women.

Materials and Methods

Study population

AACES is an ongoing, population-based, case–control study of invasive EOC in AA women in 11 locations (Alabama, Georgia, Illinois, Louisiana, Michigan, New Jersey, North Carolina, Ohio, South Carolina, Tennessee, and Texas). Institutional review board approval was obtained from all participating institutions. Methods have been described in detail elsewhere (19). Briefly, cases include AA women 20 to 79 years of age with newly diagnosed EOC. With a goal of enrolling an equal number of cases and controls, controls were AA women identified through random digit dialing, with at least one intact ovary and no history of ovarian cancer, and frequency matched to cases on region of residence and 5-year age categories. Participants complete a baseline telephone interview, which includes detailed questions on demographic characteristics; reproductive, gynecologic, and medical history; hormone therapy (HT) and oral contraceptive (OC) use; cancer family history and lifestyle characteristics including smoking, alcohol consumption, and physical activity. In an effort to obtain information from as many women as possible, a short version of the questionnaire is offered to those who would otherwise refuse to participate in the study. Accrual began in December 2010 and as of August 31, 2015, 593 cases and 750 controls were enrolled. Eligibility for this analysis was restricted to participants for whom data on body powder use and all covariates were available, resulting in a final sample size of 584 cases and 745 controls; of these, 49 cases and 16 controls completed the short questionnaire.

Exposure to body powder and talc

In the baseline interview, participants were asked whether they had ever regularly used talc, cornstarch, baby, or deodorizing powders. Participants were considered "regular users" if they reported using any of these powders at least one time per month for at least 6 months, and "never users" if they did not. Regular users were asked about their frequency and duration of use, age at first use, and whether they applied powders to genital areas (including on underwear or sanitary napkins, or on birth control devices like diaphragms) and/or nongenital areas. Participants were categorized according to their type of application as nongenital use only, genital use only, or genital and nongenital use. Lifetime number of applications was calculated by multiplying the number of body powder applications per month by the number of months used. Occupational exposure to talc (yes, no) was available only for subjects completing the long baseline survey.

Statistical analysis

The prevalence of demographic characteristics was calculated and t tests and χ^2 tests were performed to compare distributions between cases and controls. Because of the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), we merged this exposure category with those who reported use of both nongenital and genital powder, creating an exposure category of "any" genital powder use. Unconditional multivariable logistic regression was performed to calculate ORs and 95% CIs for the associations between body powder exposure ("only" nongenital use, and "any" genital use) and risk of EOC. Body powder exposure was further examined by frequency of use (less than 30 times per month, daily), duration of use categorized as less than the median or the median and greater among the controls (<20 years, $\geq$20 years), and lifetime number of applications categorized as less than the median or the median and greater among controls (<3,600, $\geq$3,600 lifetime applications). Trend tests for frequency, duration, and lifetime applications of powder use by route of exposure were conducted separately in two subsamples: only nongenital users plus never users and any genital users plus never users. For each subsample, each of the above variables was entered into a logistic regression as multiple indicator variables representing three levels and two degrees of freedom (i.e., for frequency of use: no exposure, less than daily, daily), adjusting for confounders. Trends were evaluated by statistical tests for the association between frequency/duration/lifetime applications with EOC risk, using Wald tests to simultaneously test the equality of parameter estimates with zero. Because experimental data suggest a relationship between inhaled inert particles and asthma (20), a logistic regression analysis was conducted to determine the association between body powder use and upper respiratory conditions (yes/no), controlling for EOC case/control status.

Covariates included reference age in years (age at diagnosis for cases and age at baseline interview for controls); study site [Alabama, Louisiana, New Jersey, North Carolina, Ohio, South Carolina, Texas, Michigan and Illinois (combined because of sample size and regional similarities), Georgia and Tennessee (combined because of sample size)]; education ($\leq$high school, some after high school training, college or graduate degree); parity (0, 1, 2, 3+); duration of oral contraceptives (never, <60 months, $\geq$60 months); history of tubal ligation (yes/no); family history of breast or ovarian cancer in a first-degree relative (yes/no); smoking (ever/never); and body mass index (BMI < 25, 25–29.9, $\geq$30 kg/m^2). Two class action lawsuits were filed in 2014 (21) concerning possible carcinogenic effects of body powder, which may have influenced recall of use. Therefore, year of interview 2014 or later (yes/no) was included as a covariate in the logistic regression models. To assess potential reporting bias, we also examined whether there were differences in prevalence of reported powder use by interview year (before 2014, 2014 and later) for cases and controls as well as whether interview year was an effect modifier of the relationship between powder use and EOC risk.

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Analyses by the histologic subtype versus all controls were also conducted and heterogeneity of risk estimates was tested by seemingly unrelated regression (22). Because of the missing data for histology, 48 cases were omitted from these analyses. Through stratified analyses, we also assessed possible effect modification of the association with powder use and ever use of HT among postmenopausal women using logistic regression. Experimental data show that the inflammatory response is enhanced in the presence of estrogen and progesterone and we therefore tested for interaction of the association with body powder use by menopausal status (20). Logistic regression and trend analyses were performed using SAS version 9.4 (SAS Institute).

Results

Descriptive statistics for cases and controls are presented in Table 1. Cases were older than controls and had lower educational achievement. Although this study was designed to match controls to cases by 5-year age group, the difference in the age at diagnosis/age at interview may, in part, be because the study is actively enrolling subjects. However, age ranges of cases (20–79 years) and controls (20–79 years) overlap. Significant differences in the distributions of well-established risk factors, including a shorter duration of oral contraceptive use, and lower prevalence of tubal ligation in cases as compared with controls, were as expected. As expected, parity was lower among cases compared with controls, but the difference was not significant. In addition, cases were more likely to report a family history of breast or ovarian cancer. No significant difference in the median years of use of body powder or occupational exposure of talc in cases compared with controls was observed.

Table 2 shows the results of logistic regression models examining the relationship between any use of body powder (either "only" nongenital powder or "any" genital powder) as well as the use of body powder by type of application: "only" nongenital powder use or "any" genital powder use. Adjusting for potential confounders, we observed a significant positive association between any powder use and EOC (OR = 1.39; 95% CI, 1.10–1.76). The OR for the association with "any" genital powder use was 1.44 (95% CI, 1.11–1.86). An OR of 1.31 (95% CI, 0.95–1.79) for the measure of association between "only" nongenital powder use and EOC was only slightly lower in magnitude compared with the association when "any" genital use was reported, but not statistically different from one another ($P = 0.56$). In 2014 and later, we observed an increase in any powder use of 12% and 6% of cases and controls, respectively. Although increased, these exposure prevalences were not significantly different from those interviewed before 2014 ($P = 0.30$). For those interviewed in 2014 or later, we observed an OR for "any" genital powder use of 2.91 (95% CI, 1.70–4.97) compared with 1.19 (95% CI, 0.87–1.63) before 2014. We observed a weaker OR of 1.26 (95% CI, 0.69–2.32) for 2014 and later compared with 1.40 (95% CI, 0.96–2.03) before 2014 for those who reported "only" nongenital use. A test for effect modification by year of interview was statistically significant ($P = 0.005$).

The ORs for the association between daily use of powder for either "only" nongenital powder use (OR = 1.53; 95% CI, 1.00–2.35) or "any" genital powder use (OR = 1.71; 95% CI, 1.26–2.33) with EOC were larger in magnitude than ORs for less than daily use compared with never use but the test for trend was significant for only "any" genital powder use (Table 2). There is a moderately stronger association for ≥20 years of "any" genital powder use (OR = 1.51; 95% CI, 1.11–2.06) compared with <20 years of use (OR = 1.33; 95% CI, 0.95–1.86; $P_{trend} = 0.02$). No dose–response with years of use was detected for "only" nongenital powder use. The ORs for the number of lifetime applications

Table 1. Characteristics of ovarian cancer cases and controls in the African American Cancer Epidemiology Study (AACES)

	Cases ($n = 584$) n (%)	Controls ($n = 745$) n (%)	P
Age (years)			<0.01
<40	31 (5.3)	80 (10.7)	
40–59	299 (51.21)	398 (53.4)	
60+	254 (43.5)	267 (35.8)	
Range (years)	20–79	20–79	
Education			0.02
High school or less	262 (44.9)	278 (37.3)	
Some after high school training	145 (24.8)	210 (28.2)	
College or graduate degree	177 (30.3)	257 (34.5)	
Body mass index (kg/m^2)			0.09
<24.9 (under- and normal weight)	86 (14.7)	140 (18.8)	
25–29.9 (overweight)	148 (25.3)	197 (26.4)	
>30 (obese)	350 (59.9)	408 (54.8)	
Parity (# of live births)			0.06
0	105 (18.0)	96 (12.9)	
1	113 (19.4)	141 (18.9)	
2	136 (23.3)	198 (26.6)	
3+	230 (39.4)	311 (41.6)	
Tubal ligation			0.02
Yes	201 (34.4)	302 (40.5)	
No	383 (65.6)	443 (59.5)	
Oral contraceptive use			<0.01
Never	180 (30.8)	155 (20.8)	
<60 months	230 (39.4)	334 (44.8)	
>60 months	174 (29.8)	256 (34.4)	
First-degree family history of breast or ovarian cancer			<0.01
Yes	149 (25.5)	132 (17.7)	
No	435 (74.5)	613 (82.3)	
Menopausal status			0.31
Premenopausal	158 (27.2)	221 (29.7)	
Postmenopausal	423 (72.8)	522 (70.3)	
Hormone therapy			0.10
Ever use	118 (20.3)	125 (16.8)	
Never use	463 (79.7)	618 (83.2)	
Smoking			0.48
Ever	257 (44.0)	313 (42.0)	
Never	327 (56.0)	432 (58.0)	
Hysterectomy[a]			0.43
Yes	141 (24.1)	166 (22.3)	
No	443 (75.9)	579 (77.7)	
Body powder use (median years)[b]	20	20	0.48
Occupational talc exposure[c]			0.16
Yes	58 (10.8)	62 (8.5)	
No	477 (89.2)	667 (91.5)	
Histologic subtype[d]			
Serous	393 (73.2)		
Mucinous	24 (4.5)		
Endometrioid	72 (13.4)		
Clear cell	13 (2.4)		
Other	35 (6.5)		

[a]Defined as hysterectomy 2 years prior to diagnosis for cases and 2 years prior to interview for controls.
[b]Among body powder ever users only.
[c]Data not available for participants who completed the short questionnaire (49 cases and 16 controls).
[d]Data missing on histologic subtype for 47 cases.

Table 2. Adjusted ORs for the associations between mode, frequency, and duration of body powder use and ovarian cancer in the AACES

Exposure	Cases ($n = 584$) n (%)	Controls ($n = 745$) n (%)	OR[a] (95% CI)
Body powder use			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Ever use	367 (62.8)	394 (52.9)	1.39 (1.10–1.76)
Body powder use by location			
Never use	217 (37.2)	351 (47.1)	1.00 (Referent)
Only nongenital use	119 (20.4)	140 (18.8)	1.31 (0.95–1.79)
Any genital use	248 (42.5)	254 (34.1)	1.44 (1.11–1.86)
Interview date <2014	($n = 351$)	($n = 571$)	
Never use	147 (41.9)	286 (48.4)	1.00 (Referent)
Only nongenital use	76 (21.7)	104 (17.6)	1.40 (0.96–2.03)
Any genital use	128 (36.5)	201 (34.0)	1.19 (0.87–1.63)
Interview date >2014	($n = 233$)	($n = 154$)	
Never use	70 (30.0)	65 (42.2)	1.00 (Referent)
Only nongenital use	43 (18.4)	36 (23.3)	1.26 (0.69–2.32)
Any genital use	120 (51.5)	53 (34.4)	2.91 (1.70–4.97)
Frequency of use			
Never use	217 (37.3)	351 (47.2)	1.00 (Referent)
Only nongenital use			
Less than daily	61 (10.5)	82 (11.0)	1.15 (0.78–1.71)
Daily	58 (10.0)	58 (7.8)	1.53 (1.00–2.35)
P_{trend}			0.09
Any genital use			
Less than daily	88 (15.1)	119 (16.0)	1.12 (0.80–1.58)
Daily	158 (27.2)	134 (18.0)	1.71 (1.26–2.33)
P_{trend}			<0.01
Duration of use			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
<20 years	59 (10.2)	68 (9.2)	1.37 (0.91–2.07)
>20 years	60 (10.3)	70 (9.5)	1.28 (0.85–1.93)
P_{trend}			0.13
Any genital use			
<20 years	101 (17.4)	118 (15.9)	1.33 (0.95–1.86)
>20 years	144 (24.8)	134 (18.1)	1.52 (1.11–2.07)
P_{trend}			0.02
Lifetime body powder applications			
Never use	217 (37.4)	351 (47.4)	1.00 (Referent)
Only nongenital use			
Below median (<3,600 applications)	60 (10.3)	72 (9.7)	1.35 (0.90–2.03)
Above median (>3,600 applications)	59 (10.2)	66 (8.9)	1.30 (0.86–1.97)
P_{trend}			0.14
Any genital use			
Below median (<3,600 applications)	92 (15.9)	119 (16.1)	1.16 (0.83–1.63)
Above median (>3,600 applications)	152 (26.2)	133 (17.9)	1.67 (1.23–2.26)
P_{trend}			<0.01

[a]Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

of body powder at or above and below the median support a dose–response with "any" genital powder use ($P_{trend} < 0.01$) but not for nongenital powder use ($P_{trend} = 0.14$).

A report of any occupational talc exposure, for those completing the long baseline questionnaire, was found to be positively, but not statistically significantly, associated with EOC (OR = 1.31; 95% CI, 0.88–1.93; data not shown). Table 3 shows an OR of 1.38 (95% CI, 1.03–1.85) for the association in serous cases with "any" genital powder use. Among serous cases, the OR for "only" nongenital powder use was lower in magnitude and not significant (OR = 1.10; 95% CI, 0.76–1.58). Compared with serous cases, larger and statistically significant ORs are found for the associations with type of powder application in nonserous EOC cases; ORs were 1.63 (95% CI, 1.04–2.55) and 2.28 (95% CI, 1.39–3.74), for "any" genital powder use and "only" nongenital powder use, respectively (Table 3). A comparison of adjusted odds ratios between serous and nonserous histologic subtypes and powder use, detected a difference in "only" nongenital powder use ($P = 0.008$), but did not detect significant differences in association for "any" genital powder use ($P = 0.50$).

The stratified results by menopausal status (Table 4) suggest differences in the association for exposure to "only" nongenital powder use among premenopausal where no association is seen for "only" nongenital powder use, whereas the association with the risk of EOC and "any" genital use is elevated. Among postmenopausal women, we observed positive associations of similar magnitude for both the association between EOC and "only" nongenital powder use (OR = 1.49; 95% CI, 1.04–2.15) and "any" genital powder use (OR = 1.41; CI, 1.03–1.92). However, tests of interaction indicate no evidence for interaction by menopausal status for either route of exposure. Among menopausal women, analyses stratified by HT use suggest a stronger association among users compared with nonusers of HT for both routes of applications, although we detected a borderline, nonsignificant interaction for the associations with "any" genital body powder by HT use ($P = 0.06$). The test for interaction for nongenital body powder by HT use was not significant ($P = 0.76$).

To further consider the underlying mechanism for the relationship between use of body powder and the risk of EOC, we calculated the association between both "only" nongenital powder use and "any" genital powder use and having an upper respiratory condition. Controlling for case–control status, age at diagnosis/interview, study site, education, smoking, and BMI, we found ORs of 1.35 (95% CI, 0.89–2.05) and 1.45 (95% CI, 1.03–2.05) for "only" nongenital and "any" genital powder use, respectively, in relation to a reported respiratory condition, respectively (data not shown). A nonsignificant, but elevated OR of 1.26 (95% CI, 0.77–2.06) was observed with occupational exposure to talc and respiratory conditions (data not shown).

Table 3. Adjusted ORs for the associations between talc use and serous/nonserous EOC

Histologic subtype[a]	Cases n (%)	Controls n (%)	OR[b] (95% CI)
Serous ($n = 392$)			
Never use	156 (39.8)	351 (47.1)	1.00 (Referent)
Only nongenital use	71 (18.1)	140 (18.8)	1.10 (0.76–1.58)
Any genital use	165 (42.1)	254 (34.1)	1.38 (1.03–1.85)
Nonserous ($n = 144$)			
Never use	44 (30.6)	351 (47.1)	1.00 (Referent)
Only nongenital use	42 (29.2)	140 (18.8)	2.28 (1.39–3.74)
Any genital use	58 (40.3)	254 (34.1)	1.63 (1.04–2.55)

[a]Test for interaction for association with powder use by serous and nonserous histologic subtype and route of body powder exposure was $P = 0.008$ for "only" nongenital powder use and $P = 0.50$ for "any" genital powder use.
[b]Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.

Table 4. Adjusted ORs for the association between EOC risk and body powder by menopausal status and HT use

	Premenopause			Postmenopause		
	Cases ($n = 158$)	Controls ($n = 221$)		Cases ($n = 423$)	Controls ($n = 522$)	
Exposure	n (%)	n (%)	OR[a] (95% CI)	n (%)	n (%)	OR[a] (95% CI)
Body powder use[b]						
Never use	59 (37.3)	103 (46.6)	1.00 (Referent)	157 (37.1)	247 (47.3)	1.00 (Referent)
Only nongenital use	22 (13.9)	42 (19.0)	0.90 (0.44–1.84)	97 (22.9)	98 (18.8)	1.49 (1.04–2.15)
Any genital use	77 (48.7)	76 (48.7)	1.50 (0.87–2.57)	169 (40.0)	177 (33.9)	1.41 (1.03–1.92)
HT ever/never use[c,d,e]						
HT ever use						
Never use				34 (32.1)	55 (48.7)	1.00 (Referent)
Only nongenital use				23 (21.7)	23 (20.4)	1.74 (0.77–3.92)
Any genital use				49 (46.2)	35 (31.0)	2.68 (1.33–5.40)
HT never use						
Never use				122 (38.9)	191 (46.9)	1.00 (Referent)
Only nongenital use				73 (23.3)	75 (18.4)	1.51 (0.99–2.29)
Any genital use				119 (37.9)	141 (34.6)	1.24 (0.87–1.79)

[a]Adjusted for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of OC use, first-degree family history of breast or ovarian cancer, and interview year.
[b]Test for interaction between menopausal status and route of body powder exposure was nonsignificant for only non-genital use ($P = 0.21$) and any genital use ($P = 0.85$) compared with never use.
[c]Restricted to postmenopausal women.
[d]Test for interaction between HT use and only nongenital use was nonsignificant ($P = 0.76$).
[e]Test for interaction between HT use and any genital use was nonsignificant ($P = 0.06$).

Discussion

In the largest EOC case–control study in AA women to date, we observed a positive association between regular use of powder and EOC regardless of the route of application. Users of genital powder were shown to have greater than a 40% increased risk of EOC compared with an increased risk of more than 30% among those who used only nongenital powder. The OR for the association with genital powder use in the current study is consistent with the association reported in AA women by Wu and colleagues (14). Of note, a high proportion of EOC cases (63%) and controls (53%) reported any use of body powder. A dose–response trend was evident for median years of use or greater as well as median number or greater of lifetime applications of "any" genital powder but not for use of "only" nongenital powder. Our results support that the association with "any" genital powder use is similar in premenopausal and postmenopausal women, whereas there appears to be an association with use of "only" nongenital powder use among postmenopausal but not premenopausal women. Associations were found among nonserous EOC cases and among postmenopausal users of HT exposed to either genital or nongenital powder.

Most previous case–control studies have not found an association between nongenital powder use and ovarian cancer, including a large pooled analysis by Terry and colleagues who reported an adjusted OR of 0.98 (95% CI, 0.89–1.07; refs. 6, 16). No prospective studies have evaluated nongenital powder use, nor has any study examined these associations by histologic subtype (17, 18). In the current study, the overall association with nongenital use and EOC was similar to that for genital powder use though it did not reach statistical significance possibly due to small numbers and random variation. However, we also did not find a dose–response relationship with frequency, duration, or lifetime applications of "only" nongenital powder use. Furthermore, we did not detect a significant association with use of "only" nongenital powder among serous cases, whereas the OR for the association with use of "only" nongenital powder showed over a 2-fold significant increased risk for nonserous EOC. In fact, we found a statistically significant difference between associations by subtype for "only" nongenital use. Given the inconsistency with previous published findings, it is also reasonable that underreporting genital powder use, such as abdominal powder use that reaches the genital area, may have led to a spurious result. Another possible explanation for our finding may be that there is a higher inflammatory response in AAs compared with whites (23–25). Our results also suggest that the route of powder exposure may have different effects by histologic subtype. As most high-grade serous EOC, but not nonserous subtypes, arise in the fallopian tubes (26), it is possible that direct exposure through the genital tract specifically affects this disease subtype. The association with any genital powder use and nonserous cases may be due to the overlap between genital and nongenital powder use (83% of cases and 83% of controls). We were unable to examine associations with "only" genital powder users due to sample size considerations. In contrast, nongenital powder use may be related to inhalation of the exposure through the lungs. Several large pooled analyses have demonstrated risk factor associations with inflammatory-associated exposures, such as smoking (27), endometriosis (28), and obesity (29) with nonserous histologic subtypes of ovarian cancer but not high-grade serous EOC, providing a plausible theoretical basis for differences we found in associations by histologic subtype.

Akin to talc powders, titanium dioxide (TiO_2) is another inert particle that induces an inflammatory response upon inhalation and has been considered to be "possibly carcinogenic to humans" by IARC (2). Experimental evidence of enhanced inflammation due to exposure to inert environmental particulates of TiO_2 showed inhibition of phagocytic activity of alveolar macrophages in pregnancy, and was found to be associated with increased asthma risk in the offspring of BALB/c mice exposed to TiO_2. In this study, elevated estrogen levels during pregnancy were found to contribute to the resulting asthma risk (20). Our findings also support that enhanced airway inflammation is due to exposure to inert particles.

Consistent with a recent study (15) where an association with powder use and asthma was reported, the relationship between body powder use and respiratory conditions likely reflects an enhanced inflammatory response due to powder use, suggesting a mechanism by which EOC risk is increased. Therefore, lung inhalation of powder could be a biologically plausible mechanism for the association between nongenital body powder use and increased EOC risk, particularly in nonserous EOC cases.

To further explore whether estrogen influences the inflammatory response, we performed stratified analyses by menopausal status. We did not see a difference in the association with premenopausal compared with postmenopausal use of "any" genital powder use, which is not consistent with a recent report (15) where an association with premenopausal use but not postmenopausal use was found. However, consistent with this report, we found a stronger association between "any" genital powder use and EOC among postmenopausal women who reported HT use compared with nonusers. This finding is also consistent with experimental data showing that in the presence of estrogen and/or estrogen and progesterone, the ability of macrophages to clear inert particulates is altered, enhancing the inflammatory response leading to the development of asthma in mouse offspring (20). It has also been proposed that chronic inflammation, resulting from exposure to body powder, whether through inhalation or through a transvaginal route, may exert a suppressive effect on adaptive immunity, leading to increased risk of EOC (30). These findings suggest that AA women may be particularly susceptible to exposure to body powder due to having higher endogenous estrogen levels compared with white women (31, 32). Because of the limited sample size, we were not able to evaluate associations with the timing or duration of HT use or the concurrent effects of both HT and powder use. Tests for interaction of the associations in the stratified analyses by HT use were not significant and our findings should be considered exploratory.

The results of the current study showed that genital powder use was associated with ovarian cancer risk in AA women and are consistent with localized chronic inflammation in the ovary due to particulates that travel through a direct transvaginal route. The dose–response observed for duration of genital powder use provides further evidence for the relationship between genital powder and overall EOC risk. Our data suggest that the increased risk due to use of genital powder applies to both serous and nonserous histologic subtypes of EOC. Use of "only" nongenital powder was not found to be associated with the serous subtype, but our data suggest a relationship with nonserous EOC. The association with serous EOC is consistent with several previous studies (4, 6, 14–17). Only the pooled analysis found associations with the endometrioid and clear cell subtypes (6). The association with any occupational talc exposure and EOC (OR = 1.31; data not shown), though not statistically significant, is also consistent with the results for "only" nongenital powder use and suggest other routes of exposure, aside transvaginal, may effect EOC risk.

A recent publication of data from the WHI, which did not find an association with genital talc use and ovarian cancer (18), was accompanied by an editorial that emphasized the challenges in assessing the exposure to talc due to the reliance on self-report (33). This limitation in the measurement of the exposure variables in the current study needs to be considered when interpreting our results. The possibility of differential misclassification exists in a case–control study such as AACES, especially due to heightened awareness of the exposure as a result of two recent class action lawsuits (21). Because of such publicity, we adjusted for date of interview in the analysis. However, there is still a possibility that recall bias may have caused some inflation of the ORs. Although our findings suggest that the publicity of the class action lawsuits may have resulted in increased reporting of body powder use, our data do not support that recall bias alone before 2014 versus 2014 or later would account for the associations with body powder use and EOC. It is possible that the lawsuits sharpened memories of body powder use and improved the accuracy of reported use for both cases and controls interviewed in 2014 or later. As the association with nongenital body powder use is not consistent with the published literature, the possibility of misclassification of exposure, residual confounding, or a chance finding cannot be ruled out as an explanation for the associations with nongenital powder use.

In summary, we found that the application of genital powder is associated with serous and nonserous EOC in AA women, a novel observation in this population that is consistent with some large studies in whites. Our data are consistent with the notion that localized chronic inflammation in the ovary caused by exposure to genital powder contributes to the development of EOC. Although associations with nongenital powder use and EOC have not been previously reported, we cannot rule out the possibility that this relationship may be specific to AA women. The high prevalence of exposure to both genital and nongenital body powder among AA women compared with the mostly white subjects (41%), as in the large pooled analysis (6), underscores the importance of the study's findings. The results of the current study suggest that the use of body powder is an especially important modifiable risk factor for EOC in AA women.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. American Cancer Society. Cancer facts & figures 2015; 2015.
2. World Health Organization, International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans; 2010. p. 1–413.
3. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med 1996;29:435–9.
4. Merritt MA, Green AC, Nagle CM, Webb PM. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int J Cancer 2008;122:170–6.
5. Rohl AN, Langer AM, Selikoff IJ, Tordini A, Klimentidis R, Bowes DR, et al. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ Health 2009;2:255–84.
6. Terry KL, Karageorgi S, Shvetsov YB, Merritt MA, Lurie G, Thompson PJ, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev Res 2013;6:811–21.
7. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler J, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 2000;11:111–7.
8. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. Br J Cancer 1989;60:592–8.
9. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer 1997;79:2396–401.
10. Cook RC, Fradet G, English JC, Soos J, Müller NL, Connolly TP, et al. Recurrence of intravenous talc granulomatosis following single lung transplantation. Can Respir J 1998;5:511–4.
11. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer 2004;112:458–64.
12. Whittemore AS, Wu ML, Paffenbarger RS, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol 1988;128:1228–40.
13. Wong C. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet Gynecol 1999;93:372–6.
14. Wu AH, Pearce CL, Tseng C-C, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int J Cancer 2009;124:1409–15.
15. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. Epidemiology 2016;27:334–46.
16. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.
17. Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, et al. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 2000;92:249–52.
18. Houghton SC, Reeves KW, Hankinson SE, Crawford L, Lane D, Wactawski-Wende J, et al. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst 2014;106:dju208.
19. Schildkraut JM, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al. A multi-center population-based case–control study of ovarian cancer in African-American women: the African American Cancer Epidemiology Study (AACES). BMC Cancer 2014;14:688.
20. Zhang Y, Mikhaylova L, Kobzik L, Fedulov A V. Estrogen-mediated impairment of macrophageal uptake of environmental TiO2 particles to explain inflammatory effect of TiO2 on airways during pregnancy. J Immunotoxicol 2015;12:81–91.
21. Drugwatch. Talcum powder lawsuits [Internet]; 2015 [cited 2015 Nov 11]. Available from: http://www.drugwatch.com/talcum-powder/lawsuits/
22. Hosmer D, Lerneshow S. Applied logistic regression. 2nd ed. New York, NY: John Wiley & Sons, Inc; 2000.
23. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and gender differences in C-reactive protein levels. J Am Coll Cardiol 2005;46:464–9.
24. Albert MA, Glynn RJ, Buring J, Ridker PM. C-reactive protein levels among women of various ethnic groups living in the United States (from the Women's Health Study). Am J Cardiol 2004;93:1238–42.
25. Paalani M, Lee JW, Haddad E, Tonstad S. Determinants of inflammatory markers in a bi-ethnic population. Ethn Dis 2011;21:142–9.
26. Bowtell DD, Böhm S, Ahmed AA, Aspuria P-J, Bast RC, Beral V, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. Nat Rev Cancer 2015;15:668–79.
27. Faber MT, Kjær SK, Dehlendorff C, Chang-Claude J, Andersen KK, Høgdall E, et al. Cigarette smoking and risk of ovarian cancer: a pooled analysis of 21 case-control studies. Cancer Causes Control 2013;24:989–1004.
28. Pearce CL, Templeman C, Rossing MA, Lee A, Near AM, Webb PM, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. Lancet Oncol 2012;13:385–94.
29. Olsen CM, Nagle CM, Whiteman DC, Ness R, Pearce CL, Pike MC, et al. Obesity and risk of ovarian cancer subtypes: evidence from the Ovarian Cancer Association Consortium. Endocr Relat Cancer 2013;20:251–62.
30. Cramer DW, Finn OJ. Epidemiologic perspective on immune-surveillance in cancer. Curr Opin Immunol 2011;23:265–71.
31. Pinheiro SP. Racial differences in premenopausal endogenous hormones. Cancer Epidemiol Biomarkers Prev 2005;14:2147–53.
32. Setiawan VW, Haiman CA, Stanczyk FZ, Le Marchand L, Henderson BE. Racial/ethnic differences in postmenopausal endogenous hormones: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev 2006;15:1849–55.
33. Wentzensen N, Wacholder S. Talc use and ovarian cancer: epidemiology between a rock and a hard place. J Natl Cancer Inst 2014;106:dju260.

Cancer Epidemiology, Biomarkers & Prevention

American Association for Cancer Research

Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)

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Exhibit 49

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Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer

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Chronic inflammation has been proposed as the possible causal mechanism that explains the observed association between certain risk factors, such as the use of talcum powder (talc) in the pelvic region and epithelial ovarian cancer. To address this issue we evaluated the potential role of chronic local ovarian inflammation in the development of the major subtypes of epithelial ovarian cancer. Factors potentially linked to ovarian inflammation were examined in an Australia-wide case–control study comprising 1,576 women with invasive and low malignant potential (LMP) ovarian tumours and 1,509 population-based controls. We confirmed a statistically significant increase in ovarian cancer risk associated with use of talc in the pelvic region (adjusted odds ratio 1.17, 95% CI: 1.01–1.36) that was strongest for the serous and endometrioid subtypes although the latter was not statistically significant (adjusted odds ratios 1.21, 95% CI 1.03–1.44 and 1.18, 95% CI 0.81–1.70, respectively). Other factors potentially associated with ovarian inflammation (pelvic inflammatory disease, human papilloma virus infection and mumps) were not associated with risk but, like others, we found an increased risk of endometrioid and clear cell ovarian cancer only among women with a history of endometriosis. Regular use of aspirin and other nonsteroidal anti-inflammatory drugs was inversely associated with risk of LMP mucinous ovarian tumours only. We conclude that on balance chronic inflammation does not play a major role in the development of ovarian cancer.

Key words: ovarian cancer; chronic inflammation; talcum powder

Chronic inflammation (hereafter referred to as inflammation) was first invoked as a possible mechanism leading to the development of epithelial ovarian cancer to explain observed associations between certain factors, such as use of talcum powder in the perineal region or pelvic inflammatory disease (PID) and risk of ovarian cancer.[1] The major mechanisms thought to underlie ovarian carcinogenesis, namely increased pituitary gonadotropins or incessant ovulation, do not explain such associations.

A link between inflammation and cancer in general has long been recognized. As early as 1863, Virchow noticed the presence of leukocytes in cancer tissues and suggested a possible connection between inflammation and cancer.[2] Since inflammation also represents the process by which the immune system responds to infection or irritation, however, it has been referred to as a 'double-edged sword' with acute (beneficial) inflammation distinguished from the chronic (detrimental) inflammation that may prevent a robust anti-tumour response.[3]

Indeed the most consistent evidence linking inflammation with ovarian cancer comes from the many reports that use of talc in the perineal region increases ovarian cancer risk.[4,5] It has been suggested that the association between talc use and ovarian cancer is strongest for serous tumours when compared to other less common subtypes.[4,6,7] This would be consistent with the histological similarities observed between serous ovarian cancer and mesothelioma, which is known to be caused by asbestos, and the shared

Abbreviations: ACS, Australian Cancer Study; AOCS, Australian Ovarian Cancer Study; BMI, body mass index; HPV, human papilloma virus; LMP, low malignant potential; NSAIDs, non-steroidal anti-inflammatory drugs; OC, oral contraceptive; PID, pelvic inflammatory disease; STI, sexually transmitted infection.

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chemical properties of talcum powder and asbestos. Testing various factors that are possibly related to ovarian inflammation in a case–control study, Ness *et al.*[8] found that perineal talc use and endometriosis, defined as the presence of endometrial tissue outside the uterus and associated with localised inflammation at the site of endometriotic implants, were positively associated with ovarian cancer risk. However, they saw no association with PID, which they had also expected to be associated with increased risk.[8] Extending these epidemiological analyses, McSorley *et al.*[9] recently found significantly higher circulating C-reactive protein (CRP) levels, a marker of systemic chronic inflammation, among 167 women with incident ovarian cancer risk in a multicentre nested case–control study.

The potential role of ovarian inflammation in the development of ovarian cancer remains an open question. The aim of the current study was to further examine the role of local chronic inflammation in the development of epithelial ovarian cancer overall and by histologic subtype. In addition to talcum powder use, we examined medical conditions that cause inflammation in the pelvic region, including endometriosis and PID, and we also tested the hypothesis that if inflammation causes ovarian cancer then regular use of anti-inflammatory drugs should be inversely associated with this disease.

Material and methods

Study design

The Australian Ovarian Cancer Study is an Australia-wide population-based case–control study of epithelial ovarian cancer. It includes incident cases of invasive and low malignant potential (LMP) ovarian cancer diagnosed in women (aged 18–79 years) between January 2002 and June 2005. A total of 3,553 women were identified with suspected ovarian cancer. Of these, 304 died before contact could be made, physicians refused to give consent to contact 133, usually because they were too sick or unable to give informed consent and 194 women could not be contacted. A further 167 (5%) were excluded on the basis of language difficulties (70), mental incapacity (33) and illness (64). The remaining 2,755 women were invited to participate and, of these, 2,319 (84% of those approached) agreed to take part.

Two researchers independently abstracted information on tumour site, histological subtype and tumour behaviour (invasive *vs.* LMP) from the diagnostic histopathology reports and discrepancies were resolved by consensus. For a sample of 87 women, the pathology reports and full set of diagnostic slides were reviewed by a gynaecologic pathologist and the agreement with the original abstracted data was more than 97% for tumour site, behaviour and subtype. After histopathology review, 624 women were excluded because they were found to have nonepithelial, nonovarian or benign tumours and 10 because their cancer was first diagnosed before the start of the study period. Of the final 1,685 eligible participants with invasive or LMP cancers of the ovary, peritoneum or fallopian tube, 1,576 (94%) returned a questionnaire and comprised the case population in the current study. Separate analyses were also carried out for the 994 serous, 191 mucinous, 141 endometrioid and 88 clear cell tumours (the remaining 162 tumours were of other epithelial or mixed subtypes).

Potential control participants were identified from the Australian Electoral Roll (all citizens are required by law to enrol). Controls were frequency-matched to the entire case series based on age (5-year groups) and state of residence. In all, 3,600 women were contacted. Of these, 158 were ineligible because of language difficulties ($n = 97$) or illness ($n = 61$) and 16 were unable to be contacted a second time. Of the 3,426 eligible women, 1,612 (47%) agreed to participate and returned a questionnaire. From these women, 6 were excluded because they reported a previous ovarian cancer and 97 because of a previous bilateral oophorectomy resulting in a total of 1,509 controls for study.

Study participants filled in a comprehensive health and lifestyle questionnaire, which included questions about their personal details, physical characteristics, family history, medical and surgical history, lifestyle habits and reproductive factors. To determine use of talcum powder in the perineal region, participants were asked whether they had ever used powder or talc in the genital area or on underwear or sanitary pads/diaphragm. They were asked their age at first use and years of talc use in these areas. Duration of talcum powder use prior to and after hysterectomy/tubal ligation was calculated and in all analyses perineal talc use was defined as use occurring while the reproductive tract was patent (*i.e.*, prior to hysterectomy/tubal ligation for those women who had undergone gynaecological surgery). Information on talc use under the arms or on the chest or abdomen was also collected.

To measure use of nonprescription anti-inflammatory medications, participants were given examples of the type of medication (*e.g.*, aspirin) followed by a list of the common generic and brand names. To quantify the frequency of use, participants were asked how often they had taken various medications over the past 5 years (ranging from never to as much as twice or more per day). The current analyses were restricted to medications known to suppress inflammation namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). Participants were also asked whether they had ever had any of a number of specific medical conditions and, if so, the ages at which these were diagnosed.

Ethics approval was received from the Human Research Ethics Committees at the Queensland Institute of Medical Research, Peter MacCallum Cancer Centre, University of Melbourne, all participating hospitals and cancer registries.

Statistical analysis

Risk estimates were calculated as odds ratios (OR) with 95% confidence intervals (CI). χ^2-Squared tests were used to test for differences in patient characteristics (*e.g.*, age, level of education). All significance tests were 2-sided and a p-value of less than 0.05 was taken as significant. Unconditional multiple logistic regression models were constructed to simultaneously adjust for confounding factors.

Exposures to factors of interest occurring in the 12 months prior to diagnosis for cases (or 12 months prior to first contact for controls) were excluded because the aetiological influence of very recent exposures on incident ovarian cancer is likely to be minimal and, in cases, recent behaviours may reflect the presence of subclinical disease. All models were adjusted for the categorical variables of age in 10-year groups (<50, 50–59, 60–69, ≥70), highest level of education, parity (number of pregnancies >6 months) and duration of contraceptive use (including oral contraceptive pills and contraceptive injections). Analyses of endometriosis and potential symptoms of endometriosis (painful or long periods) were also adjusted for the categorical variable of body mass index (BMI) 1 year prior to diagnosis/recruitment (≤24.9, 25–29.9, ≥30 kg/m^2). Other potential confounders that were considered for all analyses but not included in the final models since they did not substantially alter risk estimates were: income, family history of ovarian or breast cancer, hysterectomy and/or tubal ligation and smoking.

All analyses were performed using the SAS system V 9.1 (SAS Institute, Cary, NC). Tests for linear trend were performed using the maximum likelihood test with the categorical variable of interest entered as a continuous term.

Results

The final study population included 1,576 women with epithelial ovarian cancer (invasive and LMP) and 1,509 controls. Cases were significantly older than controls (mean age cases = 57.8, mean age controls = 56.42, $p = 0.001$) and were less likely to have continued their education beyond high school (Table I). As expected, cases were significantly more likely to be nulliparous

TABLE I – DESCRIPTIVE CHARACTERISTICS OF 1,576 WOMEN WITH EPITHELIAL OVARIAN CANCER AND 1,509 RANDOMLY SELECTED POPULATION-BASED CONTROLS

Variable	Controls[1] (N = 1,509) N (%)	Cases[1] (N = 1,576) N (%)	p-Value
Highest level of education			
High school	735 (49)	851 (54)	0.02[2]
Technical college/ trade certificate	550 (37)	502 (32)	
University	218 (15)	214 (14)	
Number pregnancies (≥6 months)			
Nulliparous	181 (12)	298 (19)	<0.0001[3]
1–2	644 (43)	647 (41)	
≥3	684 (45)	628 (40)	
Ever used oral contraceptives			
No	330 (22)	505 (32)	<0.0001[3]
≤5 years	361 (24)	432 (28)	
>5 years	811 (54)	619 (40)	
Previous tubal ligation	406 (27)	355 (23)	0.0003[2]
Previous hysterectomy	289 (19)	364 (23)	0.05[2]
Mother/sister with ovarian or breast cancer	195 (13)	273 (19)	0.002[2]

[1]Numbers may not sum to total because of missing data.–[2]χ^2-square test for heterogeneity, adjusted for age group (10 year categories).–[3]χ^2-square test for trend, adjusted for age group (10 year categories).

and to report a mother or sister with ovarian or breast cancer. Cases were less likely to have used oral contraceptives or to report a previous tubal ligation. Unexpectedly, cases were somewhat more likely to report a prior hysterectomy (Table I).

Ever use of talc in the perineal region (among women with patent fallopian tubes) was associated with a significant increase in risk of all types of epithelial ovarian cancer combined (adjusted OR = 1.17, 95% CI: 1.01–1.36) (Table II). Analysis by histological subtype showed that the increase in risk was strongest for serous and endometrioid tumours although it was only statistically significant for serous tumours (adjusted OR = 1.21, 95% CI: 1.03–1.44 and 1.18, 95% CI 0.81–1.70, respectively). This increased risk was seen for both invasive and LMP serous tumours (data not shown), although the association with LMP tumours was not statistically significant because of the smaller numbers. There was no clear trend of increasing risk with longer duration of use, although tests for trend were of borderline statistical significance for all cancers and the serous subgroup (p = 0.02 for both). When we considered invasive and LMP tumours separately, a modest but statistically significant increase in risk of invasive serous tumours was observed in the highest category of use (over 25 years, adjusted OR = 1.35, 95% CI: 1.06–1.72), whereas little or no increased risk was observed with less than 25 years of use. For serous LMP tumours, a modest increase in risk was observed only in the lowest duration of use category (upto 10 years, adjusted OR = 1.71, 95% CI: 1.07–2.73) with no association for over 10 years of use.

Increased risk of ovarian cancer was specifically related to talc use in the pelvic region as talc use on other body sites showed no association (OR = 1.01, 95% CI: 0.84–1.20). In contrast to the elevated risk of ovarian cancer observed with perineal talc use prior to hysterectomy and/or tubal ligation, talc use after such surgery showed no association with serous ovarian cancer risk, regardless of duration (Table II).

Prior to 1976, talcum powder was often contaminated with asbestos fibres.[10,11] To assess whether the association between use of talc and ovarian cancer risk varied over time we evaluated this separately for different age groups. Our assumption was that use of talcum powder among older women would largely have been prior to 1976 (when voluntary guidelines to prevent asbestos contamination of talcum powder were adopted) whereas a greater pro-

TABLE II – ASSOCIATION BETWEEN PERINEAL TALCUM POWDER USE (SEPARATING THE EFFECTS OF USE PRIOR TO AND AFTER HYSTERECTOMY AND/OR TUBAL LIGATION) AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] N (%)	All cases[1] N (%)	All cases (N = 1,576) OR[2] (95% CI)	Serous (N = 994) OR[2] (95% CI)	Mucinous (N = 191) OR[2] (95% CI)	Endometrioid (N = 141) OR[2] (95% CI)	Clear cell (N = 88) OR[2] (95% CI)
Perineal use of talcum powder[3]							
Never	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
Ever	635 (43)	702 (46)	1.17 (1.01–1.36)	1.21 (1.03–1.44)	1.10 (0.80–1.52)	1.18 (0.81–1.70)	1.08 (0.68–1.72)
Use pre- or no-surgery[3]							
None	835 (57)	821 (54)	1.0	1.0	1.0	1.0	1.0
>0–10 years	193 (13)	200 (13)	1.13 (0.90–1.41)	1.26 (0.98–1.63)	0.79 (0.47–1.33)	1.05 (0.59–1.85)	1.08 (0.52–2.27)
>10–25 years	214 (15)	213 (14)	1.08 (0.87–1.34)	1.03 (0.80–1.32)	1.34 (0.86–2.08)	1.14 (0.67–1.94)	0.96 (0.48–1.90)
>25 years	228 (16)	289 (19)	1.29 (1.04–1.58)	1.34 (1.06–1.68)	1.21 (0.75–1.97)	1.31 (0.80–2.16)	1.18 (0.63–2.22)
p-Value (trend)			*0.021*	*0.022*	*0.27*	*0.28*	*0.69*
Use post-surgery							
None	1,294 (88)	1,340 (88)	1.0	1.0	1.0	1.0	1.0
>0–10 years	49 (3)	50 (3)	1.08 (0.71–1.62)	1.07 (0.67–1.69)	1.39 (0.60–3.19)	0.97 (0.34–2.77)	0.64 (0.15–2.81)
>10–25 years	81 (6)	87 (6)	1.14 (0.82–1.57)	1.03 (0.72–1.48)	2.04 (1.09–3.79)	1.03 (0.45–2.32)	0.44 (0.11–1.88)
>25 years	46 (3)	46 (3)	1.00 (0.64–1.51)	1.09 (0.69–1.71)	0.91 (0.27–3.05)	0.79 (0.23–2.64)	0.43 (0.06–3.22)
p-Value (trend)			*0.61*	*0.60*	*0.12*	*0.81*	*0.16*
Ever[3] vs. never use stratified by age at diagnosis/recruitment							
<50 years	143 (23)	137 (20)	1.16 (0.86–1.57)	1.53 (1.06–2.19)	1.42 (0.89–2.25)	0.66 (0.28–1.55)	0.98 (0.41–2.29)
50–59 years	213 (33)	237 (34)	1.22 (0.93–1.59)	1.20 (0.89–1.62)	0.76 (0.46–1.26)	1.41 (0.78–2.54)	1.67 (0.88–3.15)
60–69 years	191 (30)	207 (29)	0.93 (0.70–1.23)	0.95 (0.70–1.29)	0.83 (0.49–1.40)	1.31 (0.62–2.75)	0.87 (0.40–1.85)
≥70 years	88 (14)	121 (17)	1.61 (1.10–2.36)	1.66 (1.08–2.56)	0.91 (0.42–1.97)	1.32 (0.50–3.49)	1.41 (0.58–3.35)

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age (except age-stratified analysis), education, parity and oral contraceptive pill use.–[3]Analysis restricted to use while the genital tract was unobstructed (i.e., prior to hysterectomy).

portion of use in younger women would have been after that date. Significantly elevated risks of ovarian cancer overall and for the serous subtype were seen in women who were 70 years of age or older and also among those who were less than 50 for the serous subtype only. A modest increase in risk was also observed in the 50–59 year group (nonsignificant) however no association was observed in the 60–69 year age group. Similar results were observed when invasive tumours were examined separately (the number of LMP tumours was too small to evaluate the effects by age).

Table III shows no significant association was observed between PID and risk of all subtypes of ovarian cancer combined (OR = 1.15, 95% CI: 0.85–1.57), or for the different histological subtypes. When we examined the association relative to the time elapsed since diagnosis of PID, no association with ovarian cancer risk was observed (data not shown).

A reported history of genital herpes was not associated with risk of all subtypes of ovarian cancer combined (OR = 1.17, 95% CI: 0.73–1.87). However, a significant positive association was seen with risk of serous tumours (OR = 1.65, 95% CI: 1.01–2.69; Table III), with similar nonsignificant increases observed for both invasive (OR = 1.65, 95% CI: 0.98–2.78) and LMP serous tumours (OR = 1.76, 95% CI: 0.71–4.34). For serous tumours, similar increased risks were seen for both more recent (less than 20 years) and long-term (over 20 years) infection (data not shown).

Neither HPV infection, based on self-reported history of abnormal pap smears and/or genital warts, nor a history of mumps after the age of puberty were associated with risk of ovarian cancer overall (Table III). There was also no association with mumps when we considered infection at any age (OR = 0.95, 95% CI: 0.81–1.12). There was however a suggestion that HPV infection was associated with a slightly increased risk of the endometrioid subtype (OR = 1.58, 95% CI: 1.03–2.44). Analyses considering time since the condition was first reported did not alter these results.

We found no significant association between a reported history of endometriosis and ovarian cancer risk overall (OR = 1.31, 95% CI: 0.97–1.78). However statistically significant increased risks were seen for the endometrioid and clear cell subtypes (OR = 1.85, CI: 1.02–3.38 and OR = 2.66, CI: 1.31–5.44, respectively). Because endometriosis may go undiagnosed, we also considered a reported history of potential symptoms of endometriosis (long or painful periods) however neither was associated with ovarian cancer risk (Table III). Similar results were noted when the analysis was restricted to women who had not used hormonal contraceptives. As with other medical conditions, risk estimates did not vary with time elapsed since endometriosis was first reported.

For comparison with inflammation believed to occur in close proximity to the ovaries, medical conditions associated with inflammation at other body sites were also examined (including gall stones, inflammatory bowel disease, diverticulitis, oesophagitis, gastritis and pancreatitis). None of these conditions was associated with ovarian cancer risk (data not shown).

To assess whether regular use of anti-inflammatory medications was inversely associated with ovarian cancer risk, use of aspirin and NSAIDs in the 5 years prior to study recruitment was examined. Any use of aspirin was not associated with ovarian cancer risk for all subtypes combined (OR for any *vs.* no use = 1.06, 95% CI: 0.92–1.23; Table IV) or for any of the individual subtypes. Ever use of NSAIDs in the last 5 years also had no effect on risk of all subtypes of ovarian cancer (OR = 0.88, 95% CI: 0.76–1.02). However, risk of mucinous tumours was inversely associated with any use of NSAIDs (OR = 0.69, 95% CI: 0.50–0.94) and a further decrease in risk was observed with more frequent use (p-value trend = 0.01). Separate analyses of invasive (n = 44) and LMP (n = 147) mucinous tumours demonstrated that the observed inverse association was driven entirely by LMP tumours (OR for any *vs.* no use = 0.59, 95% CI: 0.41–0.84, compared to

TABLE III – ASSOCIATION BETWEEN SELF-REPORTED MEDICAL CONDITIONS POTENTIALLY ASSOCIATED WITH INFLAMMATION OF THE OVARIES AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] *N* (%)	All cases[1] *N* (%)	All cases (*N* = 1,576) OR[2] (95% CI)	Serous (*N* = 994) OR[2] (95% CI)	Mucinous (*N* = 191) OR[2] (95% CI)	Endometrioid (*N* = 141) OR[2] (95% CI)	Clear cell (*N* = 88) OR[2] (95% CI)
PID							
Never	1,406 (94)	1,460 (93)	1.0	1.0	1.0	1.0	1.0
Ever	84 (6)	103 (7)	1.15 (0.85–1.57)	0.96 (0.66–1.38)	1.46 (0.82–2.60)	1.29 (0.66–2.52)	0.87 (0.30–2.49)
Genital herpes							
Never	1,420 (98)	1,425 (97)	1.0	1.0	1.0	1.0	1.0
Ever	35 (2)	42 (3)	1.17 (0.73–1.87)	1.65 (1.01–2.69)	0.40 (0.09–1.71)	0.32 (0.04–2.37)	0.74 (0.10–5.63)
HPV infection							
Never	1,148 (78)	1,197 (81)	1.0	1.0	1.0	1.0	1.0
Ever	317 (22)	273 (19)	0.94 (0.78–1.15)	0.92 (0.74–1.15)	0.98 (0.66–1.45)	1.58 (1.03–2.44)	0.72 (0.36–1.47)
Mumps							
Never	496 (76)	508 (75)	1.0	1.0	1.0	1.0	1.0
Ever (postpubertal)	160 (24)	164 (25)	0.96 (0.73–1.25)	1.06 (0.79–1.42)	0.78 (0.40–1.49)	0.97 (0.50–1.87)	0.81 (0.35–1.92)
Endometriosis[3]							
Never	1,413 (94)	1,431 (92)	1.0	1.0	1.0	1.0	1.0
Ever	87 (6)	124 (8)	1.31 (0.97–1.78)	1.14 (0.80–1.62)	0.89 (0.46–1.75)	1.85 (1.02–3.38)	2.66 (1.31–5.44)
Long periods[3] (>7 days)							
Never/rarely	1,174 (82)	1,173 (82)	1.0	1.0	1.0	1.0	1.0
Often	188 (13)	192 (14)	1.05 (0.83–1.31)	1.05 (0.81–1.36)	0.70 (0.40–1.22)	1.23 (0.71–2.12)	1.26 (0.62–2.53)
Always	75 (5)	62 (4)	0.79 (0.55–1.13)	0.82 (0.55–1.23)	0.78 (0.34–1.78)	0.72 (0.27–1.85)	0.83 (0.24–2.83)
Painful periods[3]							
Never/rarely	760 (52)	711 (49)	1.0	1.0	1.0	1.0	1.0
Sometimes	290 (20)	301 (20)	1.04 (0.85–1.27)	1.04 (0.83–1.31)	0.95 (0.61–1.47)	1.07 (0.65–1.75)	1.13 (0.59–2.15)
Often	404 (28)	452 (31)	1.17 (0.98–1.40)	1.17 (0.96–1.43)	1.12 (0.77–1.64)	1.12 (0.72–1.73)	1.14 (0.65–2.00)

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age, education, parity and oral contraceptive pill use.–[3]Additionally adjusted for body mass index one year prior to diagnosis.

TABLE IV – ASSOCIATION BETWEEN ANTI-INFLAMMATORY MEDICATION USE IN THE PAST 5 YEARS AND RISK OF EPITHELIAL OVARIAN CANCER

	Controls[1] N (%)	All cases[1] N (%)	All cases (N = 1,576) OR[2] (95% CI)	Serous (N = 994) OR[2] (95% CI)	Mucinous (N = 191) OR[2] (95% CI)	Endometrioid (N = 141) OR[2] (95% CI)	Clear cell (N = 88) OR[2] (95% CI)
Aspirin							
Never	772 (51)	783 (50)	1.0	1.0	1.0	1.0	1.0
Ever	730 (49)	781 (49)	1.06 (0.92–1.23)	1.06 (0.90–1.25)	0.99 (0.72–1.35)	0.92 (0.64–1.32)	0.92 (0.58–1.45)
≤1/week	612 (41)	650 (41)	1.06 (0.91–1.23)	1.05 (0.88–1.25)	0.98 (0.71–1.36)	0.98 (0.68–1.43)	0.95 (0.59–1.54)
≥2/week	118 (8)	131 (8)	1.06 (0.80–1.41)	1.11 (0.81–1.51)	1.02 (0.52–2.03)	0.56 (0.23–1.34)	0.75 (0.30–1.89)
p-Value (trend)			*0.5*	*0.4*	*0.99*	*0.4*	*0.6*
NSAIDs							
Never	625 (42)	723 (46)	1.0	1.0	1.0	1.0	1.0
Ever	878 (58)	836 (54)	0.88 (0.76–1.02)	0.93 (0.78–1.10)	0.69 (0.50–0.94)	0.76 (0.53–1.09)	0.92 (0.58–1.45)
≤1/week	653 (43)	625 (40)	0.90 (0.76–1.05)	0.94 (0.78–1.12)	0.73 (0.53–1.02)	0.73 (0.50–1.09)	0.97 (0.59–1.60)
≥2/week	225 (15)	211 (14)	0.83 (0.66–1.04)	0.90 (0.70–1.16)	0.51 (0.28–0.93)	0.84 (0.49–1.44)	0.79 (0.39–1.58)
p-Value (trend)			*0.1*	*0.3*	*0.01*	*0.3*	*0.6*

[1]Numbers may not sum to total because of missing data.–[2]Adjusted for age, education, parity and oral contraceptive pill use.

1.17, 95% CI 0.62–2.21 for invasive mucinous tumours). There was also a dose-response relationship for LMP mucinous tumours (OR for 2 or more pills per week *vs.* no use = 0.46, 95% CI: 0.23–0.91, *p*-value trend = 0.01).

Discussion

The hypothesis that chronic inflammation may lead to the development of epithelial ovarian cancer was first proposed to explain how certain factors, such as talc use in the perineal region, may be linked to increased risk of developing ovarian cancer.[1] Testing the inflammation hypothesis in a case–control study, Ness *et al*. found that proinflammatory factors, such as perineal talc use and endometriosis increased ovarian cancer risk, but others such as PID did not significantly increase ovarian cancer risk (separate analyses of individual histological subtypes of ovarian cancer were not presented).[8] Consistent with this hypothesis, McSorley *et al*.[9] recently reported a trend of increasing ovarian cancer risk with increasing levels of CRP, a marker of inflammation. However, given the lack of specificity of CRP and its association with prevalent chronic conditions, such as ischaemic heart disease,[12] it is difficult to rule out confounding as an alternate explanation for these results.[9] Until the present study, no other epidemiological studies appear to have tested the hypothesis that ovarian inflammation is associated with ovarian cancer risk. In the current study, a significantly elevated risk of ovarian cancer overall and of the serous subtype associated with perineal talc use was identified. A nonsignificant increase in risk was also seen for endometrioid tumours. Other factors that could potentially cause ovarian inflammation (such as PID, HPV infection, mumps and endometriosis) were not associated with ovarian cancer risk overall, however there was some evidence of a positive association with some of these factors in the subtype specific analyses. These results in combination with previous studies suggest that chronic inflammation is unlikely to play a major role in the development of ovarian cancer.

Focusing on talc use, we found that any use of perineal talc was associated with a small but significantly increased risk of ovarian cancer overall and specifically amongst the invasive and LMP serous tumours although no clear dose-response with increasing duration of use was identified. This finding is consistent with results of previous studies.[4,6,7,10,13,14]

As expected, ovarian cancer risk was only related to talc use in women with no surgical closure of the fallopian tubes or those who had used talc presurgery, with no association seen for talc use after tubal sterilisation or hysterectomy. Similar observations were made in previous case–control studies of ovarian cancer (all subtypes) with elevated risks observed in women who had not had a tubal ligation[4,14] or those who had used talc presurgery.[13] These former studies together with the current findings support the hypothesis that talc particles are transported to the ovaries *via* unobstructed fallopian tubes. In contrast, the Nurses' Health study found no increase in risk among women who were perineal talc users but had never had a tubal ligation.[7]

While it has been demonstrated experimentally that talc particles can reach the ovaries in humans and rodents as the result of talc use in the pelvic region,[15–17] ovarian talc particle burden in normal human ovaries is not correlated with reported exposure levels.[17] This suggests that use of only a small amount of talc may be required for some talc to reach the ovaries and increase risk of cancer.

It has been hypothesised that talc is linked to ovarian cancer development through inflammation, however evidence linking an inflammatory response with talc contamination of the ovaries is lacking. Talc-induced inflammation is unlikely to be in the formation of granulomas as these are rarely observed in human ovaries.[18,19] Other likely manifestations of talc-induced inflammation include reduced fibrinolysis, activation of neutrophils and macrophages and increased production of cytokines and growth factors, and these have been suggested to occur in the peritoneum in response to contamination by surgical glove powder.[20] Rigorous investigation of the precise biological response of the ovarian surface epithelium to perineal talc use is needed.

We also sought to determine whether possible contamination of talc with asbestos fibres, which are known to cause inflammation of epithelial tissues, could explain the observed link between perineal talc use and serous ovarian cancer. Voluntary guidelines to prevent asbestos contamination of cosmetic talc were introduced in 1976 and consequently earlier formulations were more likely to contain asbestos fibres.[10,11] Increased risk of serous ovarian cancer was not restricted to perineal talc use in the oldest age groups, who were more likely to have been exposed to asbestos-contaminated talc, but was also observed in the youngest (less than 50 years) and the 50–59 year old age group. Other studies have also reported no increase in risk of all subtypes of ovarian cancer associated with talc use before 1970[13] or before 1975.[14] These findings contrast with 2 other reports of increased risk of serous[7] and all subtypes of epithelial ovarian cancer[10] associated with earlier use of talc.

If inflammation plays a role in the aetiology of ovarian cancer then it would be expected that PID would be associated with increased risk of ovarian cancer. PID was not associated with elevated risk of ovarian tumours in our data, confirming several previous reports of no association with PID in studies of all subtypes of ovarian cancer.[8,21,22] To date there has been only one report of a significant positive association between PID and ovarian cancer.[23] Genital herpes infection was associated with a nonsignificant increased risk of invasive serous cancer in our data, although this observation was based on a small number of exposed cases (n = 27). One previous study found no association between genital herpes and ovarian cancer risk (the number of exposed cases was not reported).[8] Latent infection by herpes virus is established

in the nerve root ganglia and it is associated with a variety of initial and recurrent symptoms such as genital ulceration.[24] It is biologically plausible that inflammation associated with genital herpes infection could increase risk of ovarian cancer as Herpes simplex virus type 2 has been detected in the upper genital tract of women with acute PID[25,26] and acute salpingitis.[27] Further studies are needed to confirm this association.

HPV infection (based on reports of abnormal pap smears and/or genital warts) showed no association with ovarian cancer risk, except for the endometrioid subtype. We hypothesised that HPV infection could potentially cause ovarian inflammation as HPV DNA has been identified in the ovaries of patients with primary ovarian squamous intraepithelial neoplasia[28,29] and in the upper genital tract of patients with cervical squamous carcinoma.[30] In addition, high-risk HPV DNA has been reported in 10% of ovarian epithelial carcinomas.[31] Abnormal pap smears and genital warts are generally associated with HPV genotypes classified as high-risk and low-risk, respectively, in regards to their association with carcinogenic transformation.[32] However, separate analyses also showed no association with ovarian cancer risk.

Mumps infection (either after puberty or at any age) was not associated with ovarian cancer risk. It has been estimated that some 5% of postpubertal mumps cases are associated with clinically apparent oophoritis, which in severe cases could result in infertility caused by nonfunctional ovarian tissue.[33] We were unable to identify these particular cases in the current analysis and therefore further study is needed to examine the association between mumps oophoritis and ovarian cancer.

While endometriosis is a condition associated with localised inflammation, it is also related to changes in hormone levels (increased oestrogen unopposed by progesterone) at the site of endometriotic implants.[34] Despite this, endometriosis or potential symptoms of endometriosis (long or painful periods) were not associated with ovarian cancer risk overall, but there was an increased risk of endometrioid and clear cell subtypes among women who reported a history of endometriosis. This result was anticipated because current epidemiological evidence suggests that endometriosis is most strongly associated with the endometrioid and clear cell subtypes of ovarian cancer.[35,36]

Finally, if inflammation did promote epithelial ovarian cancer development, then it may be reasonably expected that regular use of anti-inflammatory medications would reduce risk. However, no overall association with ovarian cancer risk was observed in the current study. This supports results from 2 recent meta-analyses, which have also not shown that regular use of anti-inflammatory medications (aspirin or other NSAIDs) reduces ovarian cancer risk.[37,38] Of interest however was the apparent inverse association between NSAID use and the mucinous subtype, which was entirely driven by the LMP group. We know from other epidemiological studies that the aetiology of mucinous tumours differs in a number of ways from the other subtypes of ovarian cancer, so NSAID use may be another factor to add to this list. However, this result awaits confirmation by others.

Strengths of our study included its large size (1,576 women with ovarian cancer and 1,509 population-based controls) and Australia-wide coverage. A limitation was the low response rate for controls (47%), which could have resulted in selection bias and possibly led to an over-representation of healthy subjects among the controls. Indeed our hysterectomy rate among controls was ~5% lower than expected, but as there are no obvious links between hysterectomy and inflammation that we have not considered, we do not believe that these small differences would have affected the present results. A healthy control bias would most likely influence the analyses of medical conditions, specifically sexually transmitted infections (STIs). For example, if participating controls were less likely to have had an STI this could bias risk estimates for STIs upwards. While we saw a positive association between herpes infection and ovarian cancer risk, there was no association with other STIs suggesting that our ORs are not systematically biased. Overall, a small number of participants reported STIs and it is possible that STIs were underreported because of possible asymptomatic infection or because of the negative connotations associated with having an STI. It is also possible that controls would be more likely to underreport STIs than cases therefore potentially biasing the risk estimates upwards. Another general limitation was that analyses of medical conditions were based entirely on self-reported medical history and as a result the accuracy of these reports could not be confirmed, although self-reports of these miscellaneous conditions are unlikely to be influenced greatly by case/control status.

In summary, most factors that could potentially cause ovarian inflammation (such as PID, HPV infection, and postpubertal mumps) were not associated with a significant elevation in ovarian cancer risk in our study. In addition, the expected corollary, an inverse association with regular use of anti-inflammatory medications, was not observed. While some subtype-specific associations were observed, these were not strong and showed no coherent pattern of association within or across subtypes, aside from the well-recognised increase in risk of endometrioid and clear cell cancers among women with endometriosis. The elevation in ovarian cancer risk associated with use of talc in the perineal region that we and others have observed has been regarded as the main evidence supporting an inflammatory mechanism in the development of epithelial ovarian cancer. However, experimental evidence that perineal talc use elicits an inflammatory response in the ovaries is lacking and overall we conclude that chronic inflammation does not play a major role in the development of ovarian cancer.

Acknowledgements

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References

1. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst 1999;91:1459–67.
2. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001;357:539–45.
3. Baniyash M. The inflammation-cancer linkage: a double-edged sword? Semin Cancer Biol 2006;16:1–2.
4. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, Harlow BL. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.
5. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res 2003;23:1955–60.
6. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol 1997;145:459–65.
7. Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, Hankinson SE. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst 2000;92:249–52.
8. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 2000;11:111–17.
9. McSorley MA, Alberg AJ, Allen DS, Allen NE, Brinton LA, Dorgan JF, Pollak M, Tao Y, Helzlsouer KJ. C-reactive protein concentrations and subsequent ovarian cancer risk. Obstet Gynecol 2007;109:933–41.
10. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992;80:19–26.
11. Rohl AN, Langer AM, Selikoff IJ, Tordini A, Klimentidis R, Bowes DR, Skinner DL. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ Health 1976;2:255–84.

12. Jenny NS, Yanez ND, Psaty BP, Kuller LH, Hirsch CH, Tracy RP. Inflammation biomarkers and near-term death in older men. Am J Epidemiol 2007;165:684–95.
13. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer 1997;79:2396–401.
14. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int J Cancer 2004;112:458–64.
15. Fleming JS, Beaugie CR, Haviv I, Chenevix-Trench G, Tan OL. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. Mol Cell Endocrinol 2006;247:4–21.
16. Henderson WJ, Hamilton TC, Baylis MS, Pierrepoint CG, Griffiths K. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res 1986;40:247–50.
17. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol 1996;174:1507–10.
18. McCluggage WG, Allen DC. Ovarian granulomas: a report of 32 cases. J Clin Pathol 1997;50:324–7.
19. Wehner AP. Biological effects of cosmetic talc. Food Chem Toxicol 1994;32:1173–84.
20. van den Tol MP, Haverlag R, van Rossen ME, Bonthuis F, Marquet RL, Jeekel J. Glove powder promotes adhesion formation and facilitates tumour cell adhesion and growth. Br J Surg 2001;88:1258–63.
21. Parazzini F, La Vecchia C, Negri E, Moroni S, dal Pino D, Fedele L. Pelvic inflammatory disease and risk of ovarian cancer. Cancer Epidemiol Biomarkers Prev 1996;5:667–9.
22. Shu XO, Brinton LA, Gao YT, Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. Cancer Res 1989;49:3670–4.
23. Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev 1995;4: 447–51.
24. Ooi C, Dayan L. Genital herpes. An approach for general practitioners in Australia. Aust Fam Physician 2002;31:825–31.
25. Heinonen PK, Miettinen A. Laparoscopic study on the microbiology and severity of acute pelvic inflammatory disease. Eur J Obstet Gynecol Reprod Biol 1994;57:85–9.
26. Paavonen J, Teisala K, Heinonen PK, Aine R, Miettinen A, Lehtinen M, Gronroos P. Endometritis and acute salpingitis associated with Chlamydia trachomatis and herpes simplex virus type two. Obstet Gynecol 1985;65:288–91.
27. Lehtinen M, Rantala I, Teisala K, Heinonen PK, Lehtinen T, Aine R, Miettinen A, Gronroos P, Punnonen R, Leinikki P, Paavonen J. Detection of herpes simplex virus in women with acute pelvic inflammatory disease. J Infect Dis 1985;152:78–82.
28. Mai KT, Yazdi HM, Bertrand MA, LeSaux N, Cathcart LL. Bilateral primary ovarian squamous cell carcinoma associated with human papilloma virus infection and vulvar and cervical intraepithelial neoplasia. A case report with review of the literature. Am J Surg Pathol 1996;20:767–72.
29. Manolitsas TP, Lanham SA, Hitchcock A, Watson RH. Synchronous ovarian and cervical squamous intraepithelial neoplasia: an analysis of HPV status. Gynecol Oncol 1998;70:428–31.
30. Giordano G, D'Adda T, Gnetti L, Froio E, Merisio C, Melpignano M. Detection of human papillomavirus in organs of upper genital tract in women with cervical cancer. Int J Gynecol Cancer 2006;16:1601–7.
31. Ip SM, Wong LC, Xu CM, Cheung AN, Tsang PC, Ngan HY. Detection of human papillomavirus DNA in malignant lesions from Chinese women with carcinomas of the upper genital tract. Gynecol Oncol 2002;87:104–11.
32. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. Vaccine 2006;24 (Suppl 1):S1–S15.
33. Morrison JC, Givens JR, Wiser WL, Fish SA. Mumps oophoritis: a cause of premature menopause. Fertil Steril 1975;26:655–9.
34. Ness RB. Endometriosis and ovarian cancer: thoughts on shared pathophysiology. Am J Obstet Gynecol 2003;189:280–94.
35. Brinton LA, Sakoda LC, Sherman ME, Frederiksen K, Kjaer SK, Graubard BI, Olsen JH, Mellemkjaer L. Relationship of benign gynecologic diseases to subsequent risk of ovarian and uterine tumors. Cancer Epidemiol Biomarkers Prev 2005;14:2929–35.
36. Somigliana E, Vigano P, Parazzini F, Stoppelli S, Giambattista E, Vercellini P. Association between endometriosis and cancer: a comprehensive review and a critical analysis of clinical and epidemiological evidence. Gynecol Oncol 2006;101:331–41.
37. Bonovas S, Filioussi K, Sitaras NM. Do nonsteroidal anti-inflammatory drugs affect the risk of developing ovarian cancer? A meta-analysis. Br J Clin Pharmacol 2005;60:194–203.
38. Harris RE, Beebe-Donk J, Doss H, Burr Doss D. Aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs in cancer prevention: a critical review of non-selective COX-2 blockade (review). Oncol Rep 2005;13:559–83.

Exhibit 50

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE: JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL No. 16-2738 (MAS) (RLS)**

THIRD AMENDED EXPERT REPORT OF LAURA M. PLUNKETT, PH.D., DABT

Date: 28 May 2024

Laura M. Plunkett

Laura M. Plunkett, Ph.D., DABT

Table of Contents

I. Training and Qualifications

1. I am a pharmacologist, toxicologist, United States Food and Drug Administration (FDA) regulatory specialist and partner in a consulting company known as BioPolicy Solutions, LLC. BioPolicy Solutions has offices in Houston, TX and Ventura, CA, and is a consulting firm that works at the interface of biological science, regulatory affairs, and business decisions to provide its clients with science-based solutions to issues associated with development and marketing of existing products as well as new technologies. Before BioPolicy Solutions was formed in June of 2020, I was principal in the consulting firm known as Integrative Biostrategies (2001 to May 2020) and head of a consulting firm known as Plunkett & Associates (1997 to 2001). Attached to this report as Appendix A is a copy of my curriculum vitae.

2. I am board-certified as a Diplomate of the American Board of Toxicology. I am a member of several professional organizations and have authored or co-authored numerous scientific publications. I have over twenty years of experience in the areas of pharmacology and toxicology and have worked in both government and academic research. I have taught pharmacology and toxicology at the undergraduate and postgraduate levels.

3. I received a B.S. degree in 1980 from the University of Georgia and a Ph.D. in pharmacology from the University of Georgia, College of Pharmacy in 1984. My doctoral research was focused on the area of cardiovascular pharmacology, and specifically dealt with delineating neurochemical mechanisms responsible for the cardiac toxicity of digitalis glycosides. My training required my understanding of the mechanisms of action and basic pharmacology of drugs from all classes.

4. From June 1984 through August 1986, I was a Pharmacology Research Associate Training (PRAT) fellow at the National Institute of General Medical Sciences, Bethesda, Maryland. I worked in a neuroscience laboratory of the National Institute of Mental Health. My research focused on the role of various brain neurochemical systems involved in the control of autonomic nervous system and cardiovascular function.

5. From September 1986 to June 1989, I was an Assistant Professor of Pharmacology and Toxicology in the medical school at the University of Arkansas for Medical Sciences, Little Rock, Arkansas, where I performed basic research in the areas of neuropharmacology and toxicology as well as cardiovascular pharmacology and toxicology. I taught courses for both medical students and graduate students in pharmacology and toxicology as well as the neurosciences. As a pharmacologist, my work was directed towards understanding the biologic mechanisms of drug actions.

6. From December 1989 to August 1997, I worked for ENVIRON Corporation, first in the Arlington, Virginia office and then in the Houston, Texas office. I worked specifically within the health sciences group and most of my projects dealt with issues surrounding products or processes regulated by the FDA. During my consulting career (ENVIRON, Plunkett & Associates, and Integrative Biostrategies), I have worked on a variety of projects dealing with the regulation of products by the FDA, including human drugs (both prescription and over-the-counter drugs), veterinary drugs, biologics, medical devices, cosmetics, consumer products, dietary supplements and foods. I have advised my clients on regulatory issues and strategies for their products, designed preclinical and clinical studies for both efficacy and safety, advised clients on issues related to statements regarding efficacy and warnings for their products based on the current labeling regulations, and generally acted as a regulatory affairs staff for small companies in early stages of product development. Among the clients that I have consulted with have been cosmetic ingredient manufacturers and manufacturers of finished cosmetic products, both large and small companies. A tool and generally accepted methodology common to all my work as a consultant would be risk assessment, including many projects where risks related to exposure to chemicals in consumer products were at issue. Also, as part of my risk assessment work, I commonly review and rely on epidemiology data, as well as animal and *in vitro* data in order to assess risks to human health.

7. With respect to my experience that is directly relevant to the issues in this case, I have done a great deal of work on projects related to regulation of cosmetics and cosmetic ingredients. As part of my regulatory practice as a consultant over more than 25 years, I have consulted with cosmetic ingredient manufacturers and manufacturers of cosmetic products on issues related to ingredient safety, product safety, labeling claims, and general regulatory

compliance issues which include US regulations and regulations in other countries. These projects have been for companies of different sophistication in terms of their knowledge of cosmetic regulatory compliance. In some cases, I have worked with large companies and provided advice on the safety of ingredients used to manufacture cosmetic products. In other cases, I have given advice to the company as part of an initial commercialization process, where the client was trying to decide how to market their product, *e.g.,* as a cosmetic or a drug, as well as to determine if their product was safe for human exposure. Prior to this litigation, I have worked on the safety of talc itself. In the 1990's, I consulted with companies making condoms, which are classified as medical devices,[1] and provided scientific advice on the safety of talcum powder that was used on the surfaces of the devices as a dry lubricant. This work included my assessment of the scientific literature, including epidemiology, animal and *in vitro* studies that discussed potential adverse health effects linked to talc exposure, including both local tissue toxicity and systemic toxicity.

8. Related to the issue of cosmetic ingredient safety is the issue of determining if that ingredient is *"generally-recognized-as-safe"*, or "GRAS". In many of my projects, the issue of whether a consumer product ingredient is GRAS is critical to determining what type of toxicity testing is needed to establish that a product or an ingredient is safe for human use. Like the reviews performed on cosmetic ingredients by members of panels such as the Cosmetic Ingredient Review (CIR) panel (the role of the CIR process and its panel is discussed in more detail below), GRAS reviews that I have performed involved consideration of animal and human toxicity data, cellular and mechanistic data, human product experience reports, and the type and level of exposure that may occur when humans are exposed to the ingredient or product.

9. As a pharmacologist and board-certified toxicologist, much of my consulting work has related to understanding and explaining the mechanisms of action of chemicals of all types, as well as the toxic effects of these chemicals. I have expertise in pharmacokinetics, where I have designed clinical trials and analyzed pharmacokinetic data. I have taught pharmacology to medical students and graduate students. I have lectured to graduate students, law students and pharmacy students on FDA regulations as they apply to all types of FDA-regulated products, including cosmetics. Throughout my career, I have published dozens of peer-reviewed articles, which are

[1] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?ID=HIS

listed in my curriculum vitae (Appendix A). I have authored a book chapter on FDA pharmacovigilance practices. I have served as a peer-reviewer for medical journals in my capacity as a pharmacologist and toxicologist. In litigation, I have provided expert testimony and been qualified by both state and federal courts in the areas of pharmacology, pharmacokinetics, toxicology, risk assessment and FDA regulations. A list of my previous testimony for the past five years is included as Appendix B.

II. Information Reviewed and Methodology Employed

10. In the current case, I have been asked to provide opinions related to the human health hazards posed by exposure to talcum powder products and how those hazards relate to the regulatory requirements for marketing cosmetic ingredients and cosmetic products in the United States. I amended my original MDL report on 30 June 2021. I prepared a second amendment to my original MDL report on 15 November 2023. This is a third amendment to my original MDL report and has been prepared to address new published peer-reviewed articles that relate to opinions I have expressed in this litigation. I am prepared to provide testimony on many of the topics addressed in my earlier reports (dated October 5, 2016, August 29, 2018, November 16, 2018, June 30, 2021, and November 15, 2023), as well as opinions contained in testimony during hearings, depositions, and trials. This report contains discussion of additional documents, scientific literature, reports, and deposition testimony that has become available since preparing my original report in October 2016 and my reports dated in 2018, 2021, and 2023. To provide a general summary, the relevant materials I have reviewed during the course of continuing work in this litigation include the following:

a) scientific literature relating to the biological effects and toxic effects of talc and other constituents that are present in talc body powder;

b) the Food, Drug and Cosmetic Act (FDCA) and regulations of the U.S. Food and Drug Administration (FDA) relating to the development and marketing of cosmetic ingredients and finished cosmetic products;

c) publicly available information on safety assessments of talc and products containing talc; and

d) documents produced during the litigation that are, for example, internal company documents, depositions of company employees, reports of other experts in the litigation, or documents found on public sites.

It should be noted that most of the sources listed above are ones commonly used in my work as a pharmacologist, toxicologist, risk assessor, and United States Food and Drug Administration (FDA) regulatory specialist, including internal company documents that often outline what was known by a manufacturer concerning their product as well as outlining company policies that relate to marketing of cosmetic ingredients and cosmetic finished products in the United States. Additionally, it is important to point out that I have had access to a large database of internal company documents, documents produced as part of the discovery process in the litigation, and that I have performed my own searches of this database as part of my work on the case. In other instances, I have directed others to perform searches on my behalf. Finally, the manufacturers that are relevant to my opinions include Luzenac, a talc ingredient manufacturer that is a part of the company known today as Imerys,[2] and Johnson & Johnson, the manufacturer of finished talc body powder products, *i.e.,* Johnson's Baby Powder™. Shower to Shower™ and Shimmer™. The other group that is relevant to my opinions in this case is the trade organization for the cosmetics industry in the United States known as the Personal Care Products Council (PCPC), a group that was formerly known as the Cosmetic, Toiletry and Fragrance Association (CTFA).

11. With respect to the methodology employed in forming my opinions for this report and my earlier reports, I used standard and generally accepted methods that apply in all my work as a pharmacologist and toxicologist that is related to assessing the safety of products, both litigation and non-litigation projects. The tool I use for safety assessment is a method known as human health risk assessment. Toxicologists routinely assess risks to human health related to exposure to chemicals in the everyday environment using the risk assessment process. In fact, toxicology is the scientific core of risk assessment. Risk assessment is a methodology that has been

[2] Since 1989, Imerys Talc America, Inc. ("Imerys") or one of its predecessor companies have supplied talc to Johnson & Johnson for its talcum powder products. These predecessor companies include Cyprus Talc Corporation, Luzenac America, Inc., and Rio Tinto Group. Throughout this report, these entities should be considered synonymous with Imerys.

used for decades by a wide variety of governmental bodies to evaluate the safety of chemicals encountered in the everyday environment and to identify the potential adverse health effects from such chemical exposures. In 1983, the National Research Council (NRC) detailed the steps for risk assessment and described the methodology that is in use today as four basic steps: hazard identification, dose-response assessment, exposure analysis, and characterization of risks (NRC, 1983). As a result, risk assessment is a standard tool used by toxicologists when they are trying to determine if exposure to a chemical(s), or a product, poses a risk to human health. Therefore, as with any project I perform involving safety assessment, I use risk assessment as a tool. The methodology of human health risk assessment is a tool described in the *Reference Manual on Scientific Evidence, Third Edition* (NRC, 2011) which is a resource developed for courts when evaluating methodology used by scientists in litigation projects.

12. The first step in any risk assessment is the one I employed here, *i.e.,* identifying, collecting, reviewing, assessing, and evaluating data from the peer-reviewed scientific literature. This literature is used as the basis of the information employed in the first two steps of the risk assessment, *i.e.,* hazard identification and dose-response assessment. In this case, that literature review involved extensive searching of the published literature that described the effects of talc and talc-based products on some aspect of human health. I used available databases to systematically search the published literature for all relevant literature. The papers I identified described the effects of talc on living organisms, tissues and cells. Some of the resources I identified were textbooks and government documents that provided overviews of the human health risks associated with talc exposure. Also included in my searches were other compounds or chemicals that are constituent parts of talc-based body powders. I had to analyze and evaluate the relevant information. For this process I employed another tool and generally accepted methodology known as a "weight-of-the-evidence" assessment. A weight-of-the-evidence assessment involves evaluating individual studies and determining what the studies describe, when considered as a whole. Therefore, weight-of-the-evidence methods were critical to defining the literature that identified the hazards of talc exposure as well as defining the dose-response relationship between talc exposure and the risk of adverse health effects. The third step in a risk assessment is exposure assessment. As I am not a case-specific expert in this litigation, I was not attempting to define any specific exposure for any specific person in quantitative terms but instead

to use exposure assessment to define the type of information relevant to the product in question, a talc-based body powder. Therefore, exposure assessment involved defining the routes of human exposure that would be relevant for evaluating the risks posed by use of the powders and the type of exposure patterns that have been linked to risks posed by the use of powders. The last step in a risk assessment is risk characterization, a process where the scientist generates some statement about risk. This final step explains the outcome of the risk assessment in terms that explain the potential impact on health of the public, for example.

13. I was trained in the use of these methods as part of my undergraduate, graduate, and postdoctoral work in pharmacology and toxicology, as well as while working as a consultant in human health risk assessment. Weight-of-the-evidence methodology, is used as part of regulatory decision making by regulatory and scientific bodies such as the FDA,[3] the U.S. Environmental Protection Agency (EPA),[4] and the U.S. Occupational Safety and Health Administration (OSHA),[5] and the World Health Organization (WHO) and the International Agency for Research on Cancer (IARC).[6] The *Reference Manual on Scientific Evidence* also describes the use of weight-of-the-evidence by experts in the process of evaluating a body of data or studies.[7]

14. At the end of this report is attached a list of the published scientific articles cited throughout this report. Attached to this report as Appendix C is a complete list of all materials that I have reviewed and/or relied upon in forming my opinions in this case. All the opinions expressed in this report are based on a reasonable degree of scientific certainty. I reserve the right to

[3] *e.g.*, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079257.pdf; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf; http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079240.pdf
[4] *e.g.*, https://www.epa.gov/sites/production/files/2015-06/documents/acephate-103301_2015-06-29_txr0057153.pdf; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23160&CFID=65932199&CFTOKEN=24176705; https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=65932266&CFTOKEN=97071893
[5] https://www.osha.gov/weightofevidence/woe_guidance.pdf
[6] http://www.who.int/phe/news/events/international_conference/Session2_DrStraif.pdf
[7] The *Reference Manual on Scientific Evidence*, 3rd Edition. National Research Council. 2011. Washington, DC: The National Academies Press. https://doi.org/10.17226/13163.

supplement and refine my opinions as additional relevant information becomes available. I also reserve the right to review and comment on the reports and testimony of Defendants' experts.

III. Talcum Powder Products: The Regulatory Process

15. Johnson & Johnson talcum powder products entered the marketplace in 1894. At that time, the FDA did not exist and there was no law in place related to any type of product that is currently addressed by FDA regulations. Prompted by a series of food contamination issues, the Pure Food and Drugs Act was passed by Congress and signed into law in 1906 (Janssen 1981). This initial law was enforced by the Agriculture Department's Bureau of Chemistry and prohibited the introduction of "misbranded" and "adulterated" foods, drinks, and drugs into interstate commerce. In 1930, the Bureau of Chemistry became the Food and Drug Administration. In the decades that followed the passage of the 1906 law, scientists involved in administration of the law were confronted with a series of public safety issues that included notably a drug-related tragedy (Sulfanilamide Elixir) and a cosmetic-related tragedy (Lash-Lure). In the case of the cosmetic product, a coal tar-based eyelash dye called Lash Lure caused serious eye injuries that included blindness and one death. Yet, it was the drug-related tragedy, where 107 people died, that purportedly led to passage of Food, Drug & Cosmetic Act (FDCA) in 1938 (Berger and Berger, 2017). Before the passage of the FDCA, there was no US law that addressed cosmetic safety specifically; the FDCA extended regulatory authority to cosmetics for the first time. The provisions of the 1938 Act that brought cosmetics under the purview of the FDA have changed little over the decades, in contrast to the multiple substantive changes in the law as it relates to other FDA-regulated products (*e.g.,* drugs, foods and medical devices).

16. As discussed in a review paper written in 1978 by the Commissioner of Food and Drugs (FDA), Dr. Kennedy, the author describes the process by which regulation of various product types evolved over the decades since 1938 (Kennedy, D. 1978). Dr. Kennedy describes how FDA moved forward over the years toward greater authority over drugs and medical devices, as well as foods, but not with respect to cosmetics. He describes the need for FDA to engage in something he termed "movement backward toward the source", where such actions are ones where FDA works to eliminate a public health threat using its existing statutory and research resources. As he stated in his paper:

"It is only in regard to cosmetics-regulated through the Bureau of Foods- that FDA has been frustrated in the necessary movement backward toward the source. While the Agency is charged with assuring that cosmetics are not harmful under conditions of use and are truthfully packaged and labeled, an anomaly in the Food, Drug, and Cosmetic Act places the burden on FDA to prove harm rather than on industry to prove safety, as is true with drugs and food additives…A study conducted by the General Accounting Office (GAO) pointed out that there is increasing evidence that some cosmetic products and ingredients carry a significant risk of injury to consumers and that, despite such evidence, efforts to regulate cosmetics have been hampered by the lack of adequate legislative authority…FDA's limited ability to reach back toward the source inhibits the Agency's ability to carry out risk assessment of cosmetic ingredients." (see pages 611-612 of Kennedy, 1978).

The regulatory standards for cosmetics have remained essentially unchanged since the 1970's with some exceptions being: (1) in 1975 the FDA stipulated the need for warning statements on the label of cosmetics products and set forth the standards (March 3, 1975; 21 CFR 740); (2) in 1992 FDA initiated voluntary filing of cosmetic product composition statements for cosmetic products (57 FR 3129, Jan. 28, 1992; 21 CFR 720); (3) in 1974 FDA began voluntary registration of cosmetic manufacturing operations (39 FR 10059, Mar. 15, 1974; 21 CFR 710); and (4) in 1974 FDA required certain specifications for cosmetic labeling (39 FR 10056, Mar. 15, 1974; 21 CFR 701). As stated in 2012 testimony before Congress (CRS, 2012), *"FDA's authority over cosmetics is less comprehensive than its authority over other FDA-regulated products with regard to GMP; premarket notification, clearance, or approval; testing; and mandatory risk labeling."* The limitations on FDA authority over cosmetics is important in this case given that the Agency relies on cosmetic manufacturers and ingredient suppliers to ensure that the products marketed are safe for human use.

17. Over the years, the U.S. General Accounting Office (GAO) has been involved in evaluation of cosmetic regulations (GAO, 1978). The mission of the GAO is stated as follows: *"GAO exists to support the Congress in meeting its constitutional responsibilities and to help improve the performance and ensure the accountability of the federal government for the benefit*

of the American people."[8] In its 1978 report, the GAO provided some important observations and suggestions on how to improve the process for protecting public health. The GAO reached the following conclusions in 1978 regarding cosmetic regulations:

> *"In spite of the significant risk of injury to consumers, the Food and Drug Administration (FDA) does not have an effective program for regulating cosmetics. The act does not authorize FDA to require manufacturers to register their plants or products, file data on ingredients, file reports of cosmetic-related injuries, or test their products for safety. Also, exemptions in the act do not permit effective regulation of coal tar hair dyes. FDA has not effectively used its existing authority. For example, it has not inspected most manufacturers' plants or sampled products for compliance with the act; it has established regulations governing the use of only 11 ingredients used in cosmetics; the safety of about 25 color additives has not been established; and it has had difficulty developing appropriate tests to be used by manufacturers in evaluating safety."*

The overall conclusion reached is reflected in the title of the report: *"Lack of Authority Hampers Attempts to Increase Cosmetic Safety"*. The GAO also made recommendations that were stated as follows:

> *"The Congress should authorize the Food and Drug Administration to require cosmetic manufacturers to prove the safety of their products. Because the agency does not have enough authority to effectively regulate cosmetics, products are being marketed which may pose a hazard to consumers. About 125 ingredients available for use in cosmetics are suspected of causing cancer, and about 25 are suspected of causing birth defects. Although many of the reported adverse effects have not been verified, 30 of the ingredients are known to cause cancer in humans or animals or contain impurities known to cause cancer. The ability of these ingredients to cause toxic effects through cosmetic use has not been determined. Manufacturers do not have to determine the safety of their products before selling them or tell the Food and Drug Administration what products they are selling and what ingredients are used in them. Many manufacturers have not voluntarily given such Information to the agency. As a result, a hazardous cosmetic can be marketed until the*

[8] https://www.gao.gov/dsp/3mission.html

Food and Drug Administration obtains information to prove that the product may be injurious to users."

The discussion and findings by the GAO in 1978 are important context for understanding the responsibilities of cosmetic manufacturers and suppliers of cosmetic ingredients, such as Johnson & Johnson and Imerys, with respect to talcum powder products. The lack of FDA authority in key areas of cosmetic regulations that existed in the past, and exist even today, means that companies that market cosmetic products and ingredients must ensure that the products they sell are safe for use before they are marketed and continue to be safe for use as new scientific information becomes available.

18. With this historical context in mind, at issue in this litigation are cosmetic products known as talcum powder products. As mentioned above, current law does not require that cosmetics or cosmetic ingredients have FDA approval before they enter the market.[9] This is true despite recent changes to cosmetic law in 2022 (the Modernization of Cosmetics Regulation Act of 2022 known as MoCRA).[10] Once cosmetic ingredients and products are marketed and placed into interstate commerce, the two important laws that pertain to the industry include the FDCA and the Fair Packaging and Labeling Act (FPLA). The FDCA defines cosmetics by their intended use, in the same way that other products (*i.e.,* drugs, device, foods, *etc.*) are regulated according to their intended use. A cosmetic is defined as follows: *"The term cosmetic means (1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles; except that such term shall not include soap."* (FDCA Section 201(i)). Among the products included in this definition are skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup, cleansing shampoos, permanent waves, hair colors, and deodorants, as well as any ingredient intended for use as a component of a cosmetic product. The FPLA, enacted in 1967,

[9] https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074162.htm

[10] https://www.fda.gov/cosmetics/cosmetics-laws-regulations/modernization-cosmetics-regulation-act-2022-mocra; it should be noted that FDA has not yet codified the new provisions of MoCRA in the CFR but has issued some guidance such as the recent *Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing* (November 2023) and the *Guidance for Industry: Registration and Listing of Cosmetic Product Facilities and Products* (December 2023).

directed the Federal Trade Commission (FTC) and the FDA to issue regulations requiring that *"consumer commodities"* be labeled to disclose net contents, identity of commodity, and name and place of business of the product's manufacturer, packer, or distributor.[11] In the case of cosmetics, the FDA was given responsibility for administering the law and for issuing regulations regarding labeling for foods, drugs, devices, and cosmetics.

19. Since the FDCA does not require that cosmetics undergo any type of approval by FDA before marketing, the focus of the regulations that have existed since passage of the law in 1938 has been to ensure that cosmetics are not *"adulterated"* and *"misbranded"*. The term *"adulterated"* with respect to cosmetics means that the product or an ingredient is known to pose a risk to human health, or the product is known to be unsanitary, or the product contains a prohibited ingredient, or the product is manufactured under unsanitary conditions (Jackson, 1995). The term *"misbranded"* means that the cosmetic product has false or misleading labeling, that the labeling fails to state information required by FDA (*i.e.,* name of product, net weight or amount of product, name of the company marketing the product, ingredients listed in descending order of amount, and any warnings about safety issues that the company is aware exist), or that the product packaging is misleading to the consumer in some way in terms of what it contains. FDA has published guidance on how to label cosmetic products.[12]

20. Unlike human drug products, both prescription drug products and those sold over-the-counter (OTC), there is no risk-benefit assessment performed as a part of a decision to allow a cosmetic product to be marketed. Cosmetics are not recognized to provide any health benefit, and, as a result, any significant health risks or concerns are unacceptable for such products. In the case of a drug, both FDA and the public understand that in some cases risks can be acceptable so long as there is some benefit assessment that outweighs that risk assessment. There are some products that are both cosmetics and drugs, and in those cases, the manufacturer must comply with both cosmetic and drug regulations.

[11] https://www.ftc.gov/enforcement/rules/rulemaking-regulatory-reform-proceedings/fair-packaging-labeling-act
[12] http://www.fda.gov/downloads/Cosmetics/Labeling/UCM391202.pdf

21. It is the cosmetic manufacturer that is responsible for ensuring that its product and its ingredients are safe for use. The cosmetic ingredient supplier also has a duty to provide warnings related to the safety of the ingredients supplied to finished product manufacturers (*Federal Register* 40(42) March 3, 1975). The FDA does no testing itself. Instead, the FDA relies on companies to conduct all testing to ensure that the finished product, and its ingredients, are safe for human use. Therefore, as is stated by FDA:

> *"Companies and individuals who manufacture or market cosmetics have a legal responsibility to ensure the safety of their products. Neither the law nor FDA regulations require specific tests to demonstrate the safety of individual products or ingredients. The law also does not require cosmetic companies to share their safety information with FDA."*[13]

As a result, manufacturers have a duty to conduct whatever testing is necessary to ensure the safety of their products and ingredients. This has been confirmed in recent FDA statements as well.[14]

22. Another aspect of the FDA regulations pertaining to cosmetics that needs to be discussed is the standard for establishing a warning that would be placed on the labeling of a cosmetic product. It is important to realize that the standard for placing a warning on a cosmetic product is very different than the standard applied to products such as drugs. The standard applied to human prescription drug products in the US is as follows (21 CFR 201.57):

> *"The labeling must be revised to include a warning about a clinically significant hazard as soon as there is reasonable evidence of a causal association with a drug;* ***a causal relationship need not have been definitely established****." [**emphasis** added]*

In the case of cosmetic products and their ingredients, however, the warning standard is as follows: (21 CFR 740.1):

> *740.1 Establishment of warning statements*
>
> *(a) The label of* ***a cosmetic product shall bear a warning statement*** *whenever necessary or appropriate* to prevent a health hazard *that* ***may be associated*** *with the product.*
>
> *[**emphasis** added]*

[13] http://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074162.htm
[14] https://www.fda.gov/cosmetics/cosmetics-laws-regulations/modernization-cosmetics-regulation-act-2022-mocra

This means that, unlike drugs, cosmetics are expected to carry warnings based on a standard of a possibility of health hazard, not on having evidence of a causal association between a health effect and the cosmetic product or ingredient. Not requiring proof of a cause-and-effect relationship is consistent with FDA's policy with drugs where causation does not need to have been proven before a warning may be placed on a drug product (see 21 CFR 201.57(c)). This issue is important in the current case involving talc cosmetic products and cancer risk because of the large body of evidence that developed over the decades providing evidence of increased risk of cancer with perineal use of talc body powder products---an important health hazard. It also is important to note that use of the term "hazard" rather than "risk" by FDA in its cosmetic labeling standard means that the likelihood of the harm being discussed (*i.e.,* cancer) does not need to be understood; it only requires that the inherent properties of the substance indicate the substance is capable of harm. Based upon the totality of the evidence reviewed there is **more than a possibility of a human health hazard**; these issues will be discussed in more detail below.

23. In the case of cosmetics, this reliance on industry for product safety assessments is especially important given that there is no Center for Cosmetics at FDA. Instead, the cosmetics regulations are enforced by the Office of Colors and Cosmetics that is within the Center for Food Safety and Applied Nutrition (CFSAN). As FDA has admitted, although the FDA has ways to monitor cosmetic products, available safety information is often limited (http://www.fda.gov/AboutFDA/Transparency/Basics/ucm262353.htm). The methods available to FDA for monitoring cosmetic products include: (1) voluntary cosmetic registration program (VCRP); (2) inspections of facilities that voluntarily register with FDA; (3) surveys of product; (4) information conveyed in Cosmetic Ingredient Review (CIR) expert panel reviews;[15] and (5) spontaneous reports from consumers. In the case of the VCRP program, companies are not legally required to tell FDA anything about their products and the type of safety data that exists. Inspection of facilities is also not legally mandated, and, as acknowledged by FDA, due to limited resources *"only a few establishments are inspected each year and just a fraction of imports are physically examined".* Similarly, FDA has conducted surveys of marketed products by buying them and then

[15] Although the FDA has access to, and can evaluate, the findings of a CIR review, such as the review for talc, the FDA does not adopt CIR findings. (See deposition testimony and exhibits of Dr. Linda Loretz dated October 2, 2018)

examining them. This has mainly been done after some problem has been identified. The CIR panel process is an industry-funded process that typically is undertaken based on some impetus for review that is initiated within government, industry or the public. The spontaneous reporting by consumers to FDA is not required by law, and many consumers are unaware of the existence of the process for cosmetics.

24. There are some important constraints on FDA's authority as it relates to cosmetics. For example, any product recall of a cosmetic for a safety reason must be a voluntary action initiated by manufacturers or distributors to remove products from the market that may pose a hazard, that are marketed in a deceptive manner, or that are defective in some way (21 CFR 7.40(a)).[16] FDA can request such recalls but cannot require such recalls.

25. Unlike products such as drugs, devices and even foods, cosmetic manufacturers are not required to register the facilities where the cosmetics are manufactured.[17] This means that although FDA has the authority to inspect such facilities, unless the facility is registered, no inspections are made. In circumstances where an issue of product contamination or adulteration comes to light, FDA does have the authority to go and inspect facilities. This means that FDA is in the role of responding to problems, not preventing problems before they occur. Again, this is very different than the role FDA plays for other types of products.

26. In 1997, FDA issued guidance to industry related to Good Manufacturing Practices (GMPs) for cosmetics.[18] The guidance has been updated as late as 2013. This guidance is non-binding but does lay out FDA's thinking in terms of how to properly manufacture, ensuring that cosmetics and their ingredients are safe for use in humans. This situation is unlike other FDA regulated products where there are mandatory GMP regulations that are actively enforced by FDA (*i.e.,* in the case of drugs, devices, and even foods).

[16]https://www.fda.gov/cosmetics/complianceenforcement/recallsalerts/ucm173559.htm
[17] https://www.fda.gov/cosmetics/registrationprogram/default.htm
[18] http://www.fda.gov/Cosmetics/GuidanceRegulation/GuidanceDocuments/ucm353046.htm

27. Based on the general lack of regulatory oversight for cosmetics, it cannot be assumed that all marketed cosmetic ingredients and products are safe for human use. Additionally, it is likely that the public is unaware that FDA has strict limitations on its ability to ensure protection of public health when it comes to cosmetic products. With these regulatory limitations in mind, the chemical components of talc body powders and their hazards were considered and are discussed below with respect to the health hazards linked to the chemical components, the evidence linking cancer with exposure to chemical components of talcum powder products, and the need to provide warnings to consumers regarding health risks that may be linked to the chemical components of talcum powder products.

IV. Chemical Components of Talcum Powder Products and Their Hazards

28. The chemical nature of talc has been reviewed (*e.g.,* USEPA, 1992; IARC, 2010). Talc (CAS No. 14807-96-6), or magnesium silicate monohydrate, is a naturally occurring hydrous magnesium silicate compound with the chemical formula $3MgO{\bullet}4SiO_2$. Like other minerals, talc can be classified by its structure, which consists of water molecules trapped between silicate sheets. This structure imparts the "feel" to talc, which is often referred to as slippery on the skin. Talc crystals are formed when these sheets stack upon each other. Talc can exist in non-plate forms as well. For example, asbestiform talc exists in nature, where asbestiform means the talc is in the shape of a fiber similar to the structure of asbestos. IARC in its 2010 Monograph on talc, provides a description of talc particles as follows: "*Talc particles are normally plate-like. When viewed under the microscope in bulk samples or on air filters, they may appear to be fibres and have been identified as such. Talc may also form as true mineral fibres that are asbestiform; asbestiform describes the pattern of growth of a mineral that is referred to as a 'habit'. Asbestiform talc fibres are very long and thin and occur in parallel bundles that are easily separated from each other by hand pressure."* (IARC, 2010 at 277). The IARC Monograph also describes asbestiform talc as not the same as talc that contains asbestos; asbestiform talc is a fibrous form of talc itself (IARC, 2010 at 406). In this report the term fibrous talc may be used to differentiate this talc powder constituent from platy talc. It is important to make such distinctions because the structure of the talc particles, platy or fibrous, and the size of the talc particles, influence the toxicity potential of the talc powder.

29. As a mineral, talc is mined in countries around the world, including in the United States. Talc can be prepared to various specifications depending on the purity desired. Talcum powder products such as the ones manufactured and sold by Imerys and Johnson & Johnson were mainly platy talc but varied in their level of purity. In other words, talc powders were not 100% platy talc but contained levels of other co-occurring compounds such as talc containing asbestiform fibers (*e.g.,* talc occurring in a fibrous habit), asbestos, nickel, chromium, and cobalt. These talc components are present in nature and are found in processed talcum powders. As a result, the purity of talcum powder products is an issue important to any safety assessment. Notably talcum powder products manufactured decades ago were well known to contain asbestos as an impurity (EPA, 1992; IARC 2010; IARC, 2012). Contemporary cosmetic grade talcum powder products also have been shown to contain detectable levels of impurities that have included asbestos (Gordon *et al.* 2014). In 2009 and 2010, the FDA performed a survey where they examined 27 samples of cosmetic-grade raw talc and 34 talc-based products, including seven talc samples from Rio Tinto/Luzenac, one bottle of Shower to Shower, and one bottle of Johnson's Baby Powder, for the presence of asbestos.[19] FDA reported no detection of asbestos in the sample tested. However, as discussed by FDA: *"The results were limited, however, by the fact that only four talc suppliers submitted samples and by the number of products tested. For these reasons, while FDA finds these results informative, they do not prove that most or all talc or talc-containing cosmetic products currently marketed in the United States are likely to be free of asbestos contamination."* Additional FDA testing for the presence of asbestos in talc body powder products has occurred. In October of 2019, Johnson & Johnson recalled a lot of its talcum body powder based on FDA finding asbestos and talc fibers in one of two lots that were tested.[20] FDA also tested samples of talc-based cosmetic products for the presence of asbestos in 2020-2021 but none of the samples tested were Johnson & Johnson body powder products.[21] In 2022, FDA again tested talc-containing cosmetics for the presence of asbestos but again, no Johnson & Johnson body powder products were tested.[22] It is important to note that in addition to actions taken by the FDA, the U.S. Environmental Protection Agency (EPA) has recognized the potential human health hazard posed

[19] http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm
[20] https://www.fda.gov/cosmetics/cosmetics-recalls-alerts/fda-advises-consumers-stop-using-certain-cosmetic-products; https://www.fda.gov/media/135911/download?attachment
[21] https://www.fda.gov/media/153415/download?attachment
[22] https://www.fda.gov/media/163572/download?attachment

by the presence of asbestos as an impurity in talc. They published a Proposed Rule in May 2022 concerning a planned expansion of their risk evaluation and risk management activities related to asbestos exposure; the Rule was made Final in July 2023 (Federal Register Vol. 88, No. 141, July24, 2023 pages 47782-47806).[23]

30. I considered the FDA testing findings in light of the disclaimer related to the 2009-2010 data, which acknowledge the limited sample size, as well as the fact that one of two lots of Johnson & Johnson baby powder tested in 2019 was positive for asbestos, and the fact that baby powder samples were not part of the testing program at FDA in 2020, 2021 and 2022. As discussed in detail below, a review of internal company documents reveals that Imerys and Johnson & Johnson were aware that talcum powder products contained detectable levels of other toxic compounds that included but were not limited to fibrous talc, asbestos, silica, chromium, nickel, and cobalt. There was one additional component of talcum powder products manufactured and sold by Johnson & Johnson, a fragrance component that contained many different chemicals (discussed below as well). Therefore, women using talcum powder products for genital dusting, or for application anywhere on the body, were exposed to a mixture of chemicals, not 100% pure platy talc. As a result, when performing a talcum powder product safety assessment, studies that describe talc products of varying purity levels were relevant to the assessment.

31. In the published medical literature, there is often discussion of talc using terms such as fibrous talc, asbestiform talc, non-asbestiform talc, or tremolite. Before discussing the literature on the toxicity of talcum powder products and its associated constituents it is useful to provide some background on the terminology of the mineral components of talcum powder products. As mentioned above, talc is one of a group of hydrous magnesium silicate minerals; its chemical formula is $Mg_3Si_4O_{10}(OH)_2$. Talc can occur as platy sheets of talc but also forms bundles of fibers (*i.e.,* occur in an asbestiform habit), which consist of a group of individual elongated crystals. Asbestos is also a hydrous magnesium silicate mineral and has a chemical formula of $Mg_3Si_2O_5(OH)_4$. Like the term "talc", asbestos is the generic designation for a group of naturally occurring mineral silicate compounds that occur as fibers, either serpentine or amphibole fibers. The asbestos forms include the serpentine mineral chrysotile, and five amphibole minerals

[23] https://www.govinfo.gov/content/pkg/FR-2022-05-06/pdf/2022-09533.pdf

(actinolite, amosite, anthophyllite, crocidolite, and tremolite) (IARC, 2012). Chrysotile, lizardite, and antigorite are the three principal serpentine silicate minerals, but only chrysotile occurs in the asbestiform habit (USGS, 2001). In the amphibole series, amosite and crocidolite occur only in the asbestiform habit, while tremolite, actinolite and anthophyllite occur in both asbestiform and non-asbestiform habits. As discussed in older published literature, fibrous talc was often a term used to refer to any form of fiber in talc, including asbestos (Rohl *et al.* 1974). As a result, in this report, care was taken to use these terms when referring to the detection of fibers: asbestos, non-asbestiform talc (platy talc), and talc containing asbestiform fibers (fibrous talc). My analysis is consistent with how IARC considered the cancer risks of different forms of talc (IARC, 2010; IARC, 2012).

32. Since talc occurs as a particle in nature, the biological effects of talc, including its adverse effects or toxic effects, are related to both its chemical composition and its physical structure. This is a general principle of toxicology that relates to tissue contact with chemical particles.[24] The biological effects and toxicology of talc have been reviewed (IARC, 1987; USEPA, 1992; IARC, 2010; Health Canada, 2021). The types of effects observed depend, in part, on the route of exposure. As a mineral, talc has the propensity to produce an irritant and inflammatory response at sites of exposure (reviewed in EPA, 1992; discussed in more detail below). It is the irritant and inflammatory properties of the mineral that the scientific literature indicates underlie many of the human health risks associated with talc exposure (as reviewed in IARC, 1987; EPA, 1992; IARC, 2010; IARC 2012; discussed in more detail below). The presence of fibers in talc is important because exposure to fibers is known to cause adverse biological effects in cells and tissue. This is driven in part by the fact that the tissue response to a fiber as compared to a particle is affected by the ability of immune cells to engulf the fiber (Fubini and Fenoglio, 2007). If the fiber is long, immune cells cannot totally engulf the compound and remove the foreign material from the tissue. As a result, there are similarities in the potential adverse effects that are associated with any fibrous mineral, both talc and asbestos.

33. Given that talc used to manufacture body powders has the potential to be a mixture of toxic compounds, it is important to understand the constituents of commercially available

[24] http://ehs.unl.edu/documents/tox_exposure_guidelines.pdf

talcum powder products manufactured and sold by Imerys and Johnson & Johnson. Johnson & Johnson was aware that asbestos or asbestiform fibers were present in talc that was mined for talcum powder products (*e.g.,* JNJ000251888). When commercially available talcum powder products have been analyzed, including powders sold by Johnson & Johnson, the data has shown that the powders contain variable levels of fibers, including fibrous talc as well as fibers that were stated to be asbestos (*e.g.,* IARC, 2012; Paoletti *et al.* 1984; Blount, 1991; Mattenklott *et al.* 2007; Moon *et al.* 2011; Gordon *et al.* 2014; Anderson *et al.* 2017; Rohl *et al.* 1976; Pooley and Rowlands, 1975; Blejer and Arlon, 1973; Cralley, *et al.* 1968; Millman, N. 1947; JNJ000025132; IMERYS205540-554; IMERYS136824; IMERYS265938-993; IMERYS245144; JNJ000375389-390; IMERYS240376-378; IMERYS240406; IMERYS213431-433; JNJNL61_000052427; JNJNL61_000042576; IMERYS138505-511; IMERYS100130-150; JNJMX68_000004996-5031; JNJTALC000301172-1179; JNJ000264653-4655; JNJNL61_000033289-3292; JNJTALC000293589-591; JNJTALC000292656-657; IMERYS051370-374; IMERYS219720-722; JNJ000062359-363; JNJ000062436; JNJ000063951; JNJ000064544; JNJ000065264-266; JNJ000277941-943; JNJ000314315-316; JNJ000314406-414; JNJAZ55_000000905-948; JNJAZ55_000004563; JNJMX68_000003728; JNJMX68_000013019-020; JNJNL61_000079334; JNJMX68_000020276-282; JNJ000231304-318; IMERYS-MDL-AB_0006980; IMERYS 210136). In more recent work related to this litigation, scientists have found that samples of Johnson & Johnson body powder products that were examined contained fibrous talc (report by Longo and Rigler dated April 28, 2017[25] where 8 of 11 samples contained fibers; report by Longo and Rigler dated August 2, 2017, [26] where 15 of 30 talc samples contained fibrous talc and 17 of 30 samples contained fibrous amphiboles). Dr. Longo's testing of talcum powder samples produced in the MDL revealed that 37 of 56 samples contained asbestos and 41 of 42 samples tested were observed to contain asbestiform talc (report of Longo and Rigler dated February 1, 2019[27]). Although companies have claimed that talcum powder products manufactured after the mid-1970's were free of asbestos, asbestos fibers have been found in products in the marketplace after that time (*e.g.,* Paoletti *et al.* 1984; Blount, 1991;

[25] The report is entitled "Analysis Report: MAS Project # 14-1683 Johnson's Baby Powder Sample Set.

[26] The report is entitled "Analysis of Johnson & Johnson Baby Powder and Valiant Shower to Shower Products for Amphibole (Tremolite) Asbestos".

[27] "The Analysis of Johnson & Johnson's Historical Product Containers and Imerys' Historical Railroad Car Samples from the 1960s to the Early 2000s for Amphibole Asbestos, 2nd Supplemental Report, Longo & Rigler, MAS Analytical Services, February 1, 2019.

Mattenklott *et al.* 2007; Moon *et al.* 2011; Anderson *et al.* 2017; Egilman and Steffen, 2018; February 16, 2018 report of Longo and Rigler;[28] IMERYS095086-087; IMERYS136824; IMERYS245144; JNJ000375389-390; IMERYS213431-433; JNJNL61_000014431-14437; IMERYS219720-722). These published scientific studies, internal testing documents, and testing results by Longo and Rigler show that asbestos has been consistently present in Johnson & Johnson's talcum powder products since the mid-1950's and certainly after the 1970's when the defendants represented that asbestos had been eliminated from talcum powder products (additional support found within the exhibits and deposition testimony of Ms. Julie Pier, dated September 12, 2018; and Dr. John Hopkins, dated August 16 & 17, 2018; October 17, 2018, and November 5, 2018). The presence of asbestos was evidenced before the 1970's and continues to be to be found in test results. It is important to note that talc containing asbestiform fibers was classified in 1986 as a known human carcinogen (IARC, 1987, 2010, 2012). In IARC's most recent findings regarding asbestos and cancer (IARC, 2012) scientists explicitly stated that its findings on asbestos and cancer risk applied equally to asbestiform talc (IARC, 2012 at 219). This makes clear that IARC has classified fibrous talc as a known human carcinogen. Other regulatory authorities have addressed the cancer risk associated with fibrous talc. For example, talc containing asbestiform fibers was listed by the State of California (PROP 65) in April 1990 as a chemical *"known to the State to cause cancer"*.[29] Given that the National Institute for Occupational Safety and Health (NIOSH) has stated that there is no safe level of asbestos exposure (NIOSH, 1980), human exposure to even very low levels of asbestos increase the risk of toxic effects including cancer, a finding that also could be applied to similar fibers, such as fibrous talc.

34. With respect to asbestos as a constituent of talcum powder products, it had been known at least by the 1930's that asbestos exposure caused lung disease (*e.g.*, Cooke, 1927; Oliver, 1927; Seiler, 1928; Wood, 1929; Merewether and Price, 1930; Merewether, 1930; Gloyne, 1935). As one author described the issue of asbestos exposure and lung disease, *"**widespread recognition of asbestosis** dates from the work of Merewether and Price in 1930 [**emphasis** added]"* (Hourihane and McCaughey, 1966). Additionally, it was known at least by the 1950's that asbestos exposure

[28] The report is entitled "TEM Analysis of Historical 1978 Johnson's Baby Powder Sample for Amphibole Asbestos".
[29] https://oehha.ca.gov/media/downloads/crnr/p65list052518.pdf

could cause lung cancer (*e.g.,* Gloyne, 1935; Doll, 1955; Selikoff *et al.* 1964). Additionally, some studies have reported an increased risk of ovarian cancer in women exposed to asbestos (*e.g.,* Keal *et al.* 1960; Graham and Graham, 1967; Newhouse *et al.* 1972; Acheson *et al.* 1982; Wignall and Fox, 1982; Newhouse *et al.* 1985; Tarchi *et al.* 1994; Bulbulyan *et al.* 1999; Germani *et al.* 1999; Magnani *et al.* 2008; Bunderson-Schelvan *et al.* 2011; Camargo *et al.* 2011; Wang *et al.* 2013; Ferrante *et al.* 2017; Kim *et al.* 2024). Regulatory authorities world-wide have identified asbestos as a known human carcinogen (*i.e.,* IARC, 1987; IARC, 2012; ATSDR, 2001; NTP, 2016; Canada[30]; European Union[31]; Australia[32]). Given the well-known toxic effects and human health risks associated with asbestos, the presence of asbestos fibers in talcum powder products is a significant risk to human health.

35. There is a fragrance component added to all Johnson & Johnson talcum powder products. In the document entitled *"Defendant Johnson & Johnson Consumer Inc.'s Supplemental Answer to Plaintiffs' Second Set of Interrogatories No. 19"* dated December 21, 2017, Johnson & Johnson provided a list of fragrance chemicals that are added to Johnson's Baby Powder® products and a list of chemicals that had been added to Johnson & Johnson's Shower-To-Shower® products. Over 50 fragrance chemicals were listed as having been added to the Shower-To-Shower products while more than 130 fragrance chemicals were listed as being currently used in Johnson's Baby Powder. This means that any bottle of talcum powder sold to consumers contained many different chemicals, not simply platy talc. It should be noted that recent changes to the Johnson & Johnson website provide disclosure to consumers of what is claimed to be "100%" of their fragrance ingredients.[33] The list on the website, however, is not the same as the list provided in the 2017 documents discussed above, and the website also fails to provide information on the fragrance chemicals used in the past. Both sources of information, the 2017 document produced by Johnson & Johnson and their updated website, fail to provide specific information on the amount of each chemical component in the fragrance component of either Johnson's Baby Powder or Shower-To-Shower.

[30] https://www.canada.ca/en/health-canada/services/air-quality/indoor-air-contaminants/health-risks-asbestos.html
[31] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM%3Aem0032
[32] https://www.safeworkaustralia.gov.au/asbestos
[33] https://www.johnsonsbaby.com/our-mission/scents-fragrance

36. A review of the chemicals listed in the 2017 document reveals that, in many cases, the compounds listed are known to have toxic properties. In fact, of the fragrance chemicals listed, several have been associated with potential carcinogenic activity. These include ethenyl benzene, also known as styrene, and *p*-cresol (4-methylphenol). Styrene is a compound that has been classified by the National Toxicology Program (NTP) as "reasonably anticipated to be a human carcinogen"[34], and classified by IARC as a 2A carcinogen (probable human carcinogen)[35]. In the case of *p*-cresol, EPA has determined that it is "possibly carcinogenic to humans".[36] Other chemicals listed as being a part of the fragrance component of Johnson & Johnson talc body powders have been reviewed by IARC for cancer potential (coumarin, eugenol, d-limonene; all given a Category 3 classification of "not classifiable")[37]. A cancer risk, however, is not the only human health risk linked to the numerous fragrance chemicals present in Johnson & Johnson talc body powder products. Even a cursory search of the scientific information available on either non-governmental sites or regulatory authority sites[38] shows that most of the chemicals are known individually to have irritant properties and/or inflammatory properties when in contact with cells and tissues. Of the more than 100 chemicals included in the 2017 list of fragrance ingredients, over 70% are compounds that have been linked with some level of irritant hazard to tissues (skin, eye, mucous membranes; see Appendix D to this report; report of Dr. Michael Crowley). The issue of irritant properties will be discussed below as it relates to carcinogenesis and mechanisms for cancer linked to talc and the chemical components of talc. Yet, consumers have never been provided with information that any of the ingredients in the Johnson & Johnson fragrance posed a potential human health risk.

37. In addition to the presence of asbestos in talcum powder products and the presence of dozens of fragrance chemicals, evidence shows that the products manufactured by Imerys and sold by Johnson & Johnson contained detectable levels of heavy metals (*e.g.,* JNJ000245268-274; JNJMX68_000004996-5031; IMERYS223869-883; IMERYS265938-993; IMERYS194090-095;

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[34] https://ntp.niehs.nih.gov/ntp/roc/content/profiles/styrene.pdf; https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=74
[35] https://monographs.iarc.fr/list-of-classifications-volumes/
[36] https://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=196
[37] https://monographs.iarc.fr/wp-content/uploads/2018/06/ClassificationsAlphaOrder.pdf
[38] Searches of publicly available databases were performed including TOXNET, PUBCHEM, HSDB, The Good Scents Company (www.thegoodscentscompany.com), the Environmental Working Group (https://www.ewg.org/), cosmeticsinfo.org (PCPC sponsored site), and the Cosmetic Ingredient Review (https://www.cir-safety.org).

IMERYS032928; IMERYS094601; IMERYS053387-88; IMERYS098115-116; IMERYS219720-722; IMERYS304036; IMERYS-A_0015663; JNJ000265171; JNJTALC000869376; JNJ000025132; JNJ000347962-963; P-68; exhibits and deposition testimony of Ms. Julie Pier dated 9/12/2018; Cralley *et al.* 1968; Pooley and Rowlands, 1975; Rohl *et al.* 1976; Gondal *et al.* 2012; Rehman *et al.* 2013) as well as levels of silica (JNJ000260573 through 574; NJN000260570; JNJ000260709). The levels of heavy metals have varied across different processed lots of talcum powders, but internal company documents show that certain heavy metals have been repeatedly detected, such as chromium (Cr), cobalt (Co), and nickel (Ni). These heavy metals are known to be toxic to human cells and tissues. Some of these heavy metals are known to be carcinogenic in animals and/or humans. Chromium (Cr) and nickel (Ni) have been classified as *"known human carcinogens"* by IARC[39]. Cobalt (Co) has been classified by IARC as Group 2B, or *"possibly carcinogenic to humans"*.[40] The NTP has listed chromium (Cr) and nickel (Ni) as *"known to be human carcinogens"*, while cobalt is listed as *"reasonably anticipated to be human carcinogens"*. [41] With respect to silica, levels also appeared to vary across lots. Like asbestos and fibrous talc, silica is a known human carcinogen (IARC, 1997; IARC, 2012; NTP, 1991).

38. Focusing now on talc itself as a toxic compound, a review of the scientific literature reveals that in many cases, the compound being tested or discussed is usually described simply as talc, with no description of the purity or physical state of the compound (fibrous or platy). In the following discussion of the literature that relates to the toxicity of talc, I will mention the specific type of talc (*i.e.,* mined talc, milled talc, fibrous talc, talc of certain purity levels, cosmetic grade talc, *etc.*), if reported.

39. A review of the published scientific literature shows that the human health hazards associated with exposure to talc dust has been known for decades, well before the 1970's. In fact, as far back as the first half of the 20th century (before 1950), scientists had discovered that:

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[39] https://monographs.iarc.fr/wp-content/uploads/2018/06/ClassificationsAlphaOrder.pdf
[40] https://monographs.iarc.fr/wp-content/uploads/2018/06/ClassificationsAlphaOrder.pdf
[41] https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf

- talc particles produced adverse tissue reactions in cells or tissues, and in humans and animals (*e.g.,* tremolite talc: Dreessen, 1933; Miller and Sayers, 1936; Greenburg, 1947; mining talc: Porro *et al.* 1942; Porro and Levine, 1946; Schepers and Durkan, 1955; industrial grade talc: Schulz and Williams, 1942; McLaughlin *et al.* 1949; Jaques and Benirschke, 1952; Sax, 1957; cosmetic grade talc: Roberts, 1947; Saxen and Tuovinen, 1947; Eiseman *et al.* 1947; U.S. Patent No. 2,621,333 filed June 27, 1947; Eberl *et al.* 1948; Graham and Jenkins, 1952; U.S. Patent No. 2,626,257 filed May 21, 1952 by Johnson & Johnson; Cless and Anger, 1954; Creery *et al.* 1957; Sax, 1957);
- exposure to talc dusts in an occupational setting was linked to an increased risk of lung disease, including cancer (*e.g.*, tremolite talc: Dreessen, 1933; Greenburg, 1947; mining talc: Dreessen and Dalla Valle, 1935; Porro *et al.* 1942; Porro and Levine, 1946; Kleinfeld *et al.* 1955; Schepers and Durkan, 1955; industrial grade talc: McLaughlin *et al.* 1949; Hogue and Mallette, 1949; Jaques and Benirschke, 1952; Mann and Deasy, 1954; Seeler *et al.* 1959; cosmetic grade talc: Millman, 1947);
- the risks associated with occupational exposures to talc were higher when fibrous forms of magnesium silicate minerals (talc as well as asbestos) were present (*e.g.*, Dreessen and Dalla Valle, 1935; Schulz and Williams, 1942; Saxen and Tuovinen, 1947; Millman, 1947; Greenburg, 1947; Hogue and Mallette, 1949; Schepers and Durkan, 1955); and
- exposure to cosmetic grade talcum powders themselves were associated with adverse tissue responses and adverse human health effects, including cancer in some cases (*e.g.,* Roberts, 1947; Greenburg, 1947; Eiseman *et al.* 1947; U.S. Patent 2,621,333; Eberl, 1948; Graham and Jenkins, 1952; U.S. Patent No. 2,626,257; Cless and Anger, 1954; Creery *et al.* 1957).

40. Upon review of the scientific literature available since 1960, the evidence has continued to accumulate showing that:

- talc has adverse effects in cells, tissues, animals and humans (*e.g.,* cosmetic grade talc: Molnar *et al.* 1962; Blumel *et al.* 1962; Jenkins, 1963; Tye *et al.* 1966; Trautwein and Helmboldt, 1967; Migaki and Garner, 1969; Merliss, 1971; Pott and Friedrichs, 1972; Wagner *et al.* 1975; Stenback and Rowland, 1978; Kaiser *et al.* 1982; Davies *et al.*

1983; Hamilton *et al.* 1984; Stenback *et al.* 1986; Pelling and Evans, 1986; NTP, 1993; Hamilton *et al.* 2001; Buz'Zard and Lau, 2007; Shukla *et al*. 2009; Shim *et al.* 2015; Fletcher *et al.* 2018; Fletcher and Saed, 2018; Fletcher *et al.* 2019; Mandarino *et al.* 2020, Harper *et al.* 2021; Emi *et al.* 2021, ; mining or milling talc: Kleinfeld *et al.* 1963; Beck *et al.* 1987; unspecified: Henderson *et al.* 1971; Blejer and Arlon, 1973; Pott *et al.* 1974; Henderson *et al.* 1979; Abraham and McEuen, 1986);

- exposure to talc dusts in an occupational setting was linked to an increased risk of lung disease, including cancer (*e.g.*, mining or milling talc: Kleinfeld *et al.* 1963; Kleinfeld *et al.* 1964; Kleinfeld *et al.* 1967; Kleinfeld *et al.* 1973; Rubino *et al.* 1976: cosmetic grade talc: Miller *et al.* 1971; Nam and Gracey, 1972);
- the risks associated with occupational exposures were higher when fibrous forms of magnesium silicate minerals (talc as well as asbestos) were present (*e.g.*, Kleinfeld *et al.* 1963; Kleinfeld *et al.* 1964; Pott and Friedrichs, 1972; Blejer and Arlon, 1973; Pott *et al.* 1974; Wagner *et al.* 1975; Stanton *et al.* 1981), being linked to fibrotic diseases of the lungs, such as talcosis and pneumoconiosis (*e.g.,* Dreesen and Dalla Valle, 1935; Porro and Levine 1946; Greenburg, 1947; Kleinfeld *et al.* 1973); and
- exposure to cosmetic grade talcum powders themselves were associated with adverse tissue responses and adverse human health effects, including deaths in some cases (*e.g.,* Molnar *et al.* 1962; Blumel *et al.* 1962; Jenkins, 1963; Hughes and Kalmer, 1966; Migaki and Garner, 1969; Moss, 1969; Miller *et al.* 1971; Nam and Gracey, 1972; Wagner *et al.* 1975; Brouillette and Weber, 1978; Mofenson *et al.* 1981; Cramer *et al.* 1982; Kaiser *et al.* 1982; Pelling and Evans, 1986; Kupryjanczyk, 1989; Buz'Zard and Lau, 2007; Shukla *et al.* 2009; Shim *et al.* 2015).

Also relevant to this discussion of what was known based on review of studies published in the scientific literature is the fact that Johnson & Johnson itself published a review article in 1976 (Hildick-Smith, 1976). In that paper, Dr. Hildick-Smith provided a summary of the scientific literature from the 1940's to the 1970's, listing many studies that provide proof that talc has toxic properties at certain doses and by different routes of exposure, *i.e.,* talc itself is a toxic compound.

41. Considered together, there is a large body of reliable scientific information, of all types (studies in cells, tissues, animals and humans), that identifies talcum powder products as posing a hazard to human health. The types of toxicity produced are dependent on the route of exposure and the purity of the talc product. Yet, there is no controversy concerning the existence of a hazard and a need to control exposures to talc dusts and powders. Exposure to talc body powders internally (direct tissue contact) can cause a variety of adverse effects that are related to the known irritant and inflammatory properties of talc itself as well as the presence of other chemical components that exist in cosmetic grade talcum powder products. It is important to note as well that in 2007, the Canadian government took action to require warning on talc product labeling for cosmetics that warned of the dangers of inhaling talc particles. Then, in 2018, Canadian regulators performed a new risk assessment for talc and published its findings in both draft (December 2018) and final (April 2021) form. As described in those documents, Canadian authorities in two agencies, Environment and Climate Change Canada and Health Canada, found that talc exposure posed a risk to human health, leading Canada to initiate actions to amend the talc listing on its cosmetic ingredient Hotlist as it relates to perineal use of talc body powders.[42] The amendments to the Hotlist for talc are still ongoing as of the date of this report.

V. Talcum Powder Products: Perineal Application and Internal Exposure

42. The human health concern with talcum powder products in the current case is ovarian cancer in women who applied the products repeatedly to the perineal area. The first step to consider in the process of producing ovarian cancer with perineal talc dusting is exposure. Although dermal exposure is also a potential route of concern, the absorption of talc particles across skin has been assumed to not be of consequence when assessing toxicity of talcum powder products unless the skin has been damaged in some way. Instead, exposure assessments of talc applied dermally have focused on entry into the body through portals such as the lungs, the vagina or the mouth (IARC, 1987; EPA, 1992; IARC, 2010). The toxicity potential of talc has been shown to be affected by the route of exposure, with more significant toxicity linked to penetration of small talc particles into tissues and triggering of cytotoxic responses at the local site of tissue interactions (EPA, 1992). Therefore, consistent with existing data, talc would be less toxic following oral

[42] https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/risk-management-approach-talc.html

exposure where the interaction with stomach acids, and presence of the gastrointestinal barrier, would affect the expected toxicity potential.

43. When assessing the potential for human exposure to talc applied to the perineal area, the focus has been on entry into the body through the vagina. There also is evidence that application of talcum powder products results in inhalation exposure of talc dusts (*e.g.,* the September 2017 study by Longo and colleagues entitled *"Below the Waist Application of Johnson & Johnson Baby Powder"*; Jasuja *et al.* 2017; Frank and Jorge, 2011; van Huisstede *et al.* 2010; Wells *et al.* 1979). An early study by the National Institute of Occupational Safety and Health (NIOSH) in 1972 showed that talcum powder products samples available commercially contained fibers and that exposure to fibers would occur during diapering (JNJ000231304-318); this study was received by Johnson and Johnson at least by March of 1974. Based on its chemical nature, talc delivered as a powder in consumer products can be inhaled while being applied (EPA, 1992; IARC, 2010). Regardless of the portal of entry, lungs versus the vagina, talc-induced local tissue toxicity would be expected to be produced in tissues that are accessed following perineal dusting with talc. With respect to inhalation exposure of talcum powder products and the potential for inhaled particles to migrate to the ovaries, studies have shown that asbestos fibers can move from the lung to other body organs via the lymphatic system (Suzuki and Kohyama, 1991; Bunderson-Schelvan *et al.* 2011). The lymphatic system is known to be involved in the transport of inhaled particles from the lung to distant sites (Leak, 1980; Stuart, 1984; Adamson and Prieditis, 1998; JNJ000046293). Thus, it is biologically plausible that talc particles that embed or deposit within lung tissue could be transported away from the lungs through the lymphatic system in the same way that other particles, and even asbestos, have been shown to travel to sites distant from their portal of entry, the lungs. With respect to genital dusting of talcum powder products, I considered the available evidence related to the ability of talc to migrate from the site of application, *i.e.,* perineal or vaginal application, to the ovaries. When considering that evidence, it is important to note that there are often misconceptions about female anatomy with respect to the vagina as an entry point for chemicals and particles. In fact. it is important to consider the following discussion of the anatomy of the female reproductive tract (Alexander *et al.* 2004):

> *"A common misperception is that the vagina is a straight tube pointing upward to the sacral promontory. Most illustrations (in both patient and clinician educational materials)*

are inaccurate and perpetuate this image. They give the impression that items placed in the vagina could easily fall out…Radiographic colpography (18, 19) has shown that the vagina is normally a curved organ with two distinct portions: a lower convex portion and a wider upper portion that lies in an almost horizontal plane when the woman is standing. The angle between the upper and lower axes is 130 degrees".

44. The migration of talc internally after perineal application was discussed by scientific and regulatory bodies that reviewed the toxicokinetics of talc (EPA, 1992; IARC, 2010) as well as by FDA in a recent letter (P-47). As FDA concluded in 2014, *"…**the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity is indisputable**. It is, therefore, plausible that perineal talc (and other particulate) that reaches the endometrial cavity, Fallopian Tubes, ovaries and peritoneum may elicit a foreign body type reaction and inflammatory response that, in some exposed women, may progress to epithelial cancers." [**emphasis** added]*. A review of the scientific literature revealed that FDA's conclusion is supported by a variety of studies that include, but are not limited to, studies examining or reviewing the migration of particles in humans (*i.e.,* Egli and Newton, 1961; de Boer, 1972; Parmley and Woodruff, 1974; Venter and Iturrulde, 1979; Blumenkrantz *et al.* 1980; Gardner *et al.* 1981; Iturralde and Venter, 1981; Halme *et al.* 1984; McCalley *et al.* 1985; Wright *et al.* 1996; Kunz *et al.* 1996; Heller *et al.* 1996; Kunz *et al.* 1997; Kadanali *et al.* 2001; Kunz and Leydendecker, 2002; Kissler *et al.* 2004; Sjosten *et al.* 2004; Kunz *et al.* 2007; Zervomanolakis *et al.* 2007; McDonald *et al.* 2019a; McDonald *et al.* 2019b; Johnson *et al.* 2020). Additionally, authors have described the potential for abdominal exposure to talc particles following perineal application of talcum powder products in women (Longo and Young, 1979); the abdominal cavity in humans is reached directly through migration of particles from the vagina, through the reproductive tract and up towards the ovaries, which are suspended within the peritoneal space. These studies are important because they demonstrate that inert particles routinely move from the lower female reproductive tract (vagina) up into fallopian tubes and towards the ovaries. There also are data demonstrating the presence of talc particles in the ovaries of women who had reported use of talcum powder products on the genital area (*e.g.,* Heller *et al.* 1996; Cramer *et al.* 2007), as well as animal studies showing that in some species talc can migrate from the lower to the upper genital tract (*e.g.,* Phillips *et al.* 1978; Gardner *et al.* 1981; Henderson *et al.* 1986; Edelstam *et al.* 1997).

Given the differences between animals and humans in terms of anatomy of the genital tract, the studies in humans are the most reliable in terms of human health risk assessment and the toxicokinetics of talc applied externally to the perineal area. The weight-of-the-evidence shows that inert particles routinely move from the lower female reproductive tract (vagina) up into the uterus, the fallopian tubes and towards the ovaries. Therefore, in terms of the potential for exposure following perineal application of talc body powders, the available data support statements by the FDA that particulates can move from the vagina up the reproductive tract in women to provide for exposure to internal organs, including the ovaries.

45. An early study examining the issue of migration of substances through the female reproductive tract was undertaken to better understand the time relationships and precise mechanisms of transport of inert particles or spermatozoa in humans (Egli and Newton, 1961). The study was designed to determine whether, under reasonably controlled conditions, carbon particles could be transported quickly from the vagina to the fallopian tubes. Three women who were scheduled for hysterectomy voluntarily participated and were administered carbon particles under anesthesia after being positioned on their backs. Three to four milliliters of sterile carbon particles in a Dextran suspension were deposited in the upper portion of the vagina. Oxytocin was administered intra-muscularly at that time as well. Immediately after injection, the fallopian tubes were removed and examined for the presence of carbon particles; a very short time was allowed for potential transport. In two of the three women, carbon particles were recovered from the fallopian tubes 28 and 34 minutes after injection into the vagina. The authors concluded: *"These data, together with other work in animals and humans, support the belief that the motility of spermatozoa is not the chief factor in sperm transport.* ***Contractions of the muscle of the uterus or other reproductive organs may be very important****, and it is possible that oxytocin may play a part in this process."[****emphasis*** *added]* A similar study was performed a decade later (DeBoer, 1972) where the author reported on the movement of carbon material up the genital tract in a series of patients undergoing abdominal surgical procedures. The women were injected (some cervical instillations and some uterine instillations) with a colloidal carbon suspension (India ink), and in some cases women also were given an injection of oxytocin. Surgeries were performed at various times after injection, from 15 minutes l to 24 hours after injection. The authors stated *"...****there was no doubt that the inert carbon material was frequently and rapidly transported from the***

***uterus to the tubes** in both phases of the menstrual cycle." [**emphasis** added]* Passage of particles from the vagina to the uterus was observed in two of 37 patients examined, while particles were detected in the fallopian tubes in 30% of patients with cervical instillation and in 50% of patients with uterine instillation. Two years later, the migration of environmental substances externally in women was discussed in connection with the origins of ovarian mesotheliomas (Parmley and Woodruff, 1974). In the discussion section the authors stated: *"The uniqueness of the female peritoneal cavity is that **environmental substances may more easily reach it by passage through the vagina and Fallopian tubes** (Fig. 13). Conversely, no such entry is available in the male…" [**emphasis** added]* All three of these studies provided early notice of the ability of particles to move up the female reproductive tract.

46. In addition to studies in humans, experiments were conducted in different animal species to examine the ability of talc to be distributed beyond the site of exposure, oral or intra-vaginal application (Phillips *et al.* 1978). As discussed by the authors, their studies were prompted by the safety concerns raised in the scientific literature with respect to talc, specifically they indicate that *"the possibility of a causal relationship between particular types of tumours and the presence of talc has caused disquiet about its safety-in-use"*. With respect to the issue of movement of talc within the reproductive tract, rabbits were administered either a single intra-vaginal dose (50 mg total talc in 0.5 ml volume; three rabbits tested) or six daily doses of the same amount of talc (also 3 rabbits). In all cases, the animals were sacrificed 72 hours after the dosing ceased. The urogenital tracts were dissected to determine if radioactivity could be detected. After one dose of radiolabeled talc, radioactivity was detected only in the vagina. In the rabbits administered multiple doses of radiolabeled talc, radioactivity was detected at the site of application but also in the cervix, the uterus and the fallopian tubes, but not the ovaries. Thus, migration or translocation occurred in the rabbit reproductive tract to a limited extent, although not all the way to the ovaries. Even though studies in animals are not ideal in terms of modeling the female reproductive tract, this study again provided notice of the ability of particles to move within the reproductive tract.

47. In another human study in 1979, scientists reported use of a radionuclide procedure designed to evaluate the migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries, as well as the determination of the patency of the pathways between

these two extremes of the female reproductive system (Venter and Iturralde, 1979). The procedure employed radiolabeled human albumin microspheres that were deposited into the vaginas of 24 patients one day before they were to undergo a gynecological surgery. Sequential images were obtained during the 24-hour period, and after the surgeries were completed radioactivity levels in the removed organs and tissues were counted with a scintillation detector. The authors reported that in 14 out of 21 cases it was possible to measure radioactivity levels in the adnexa (*i.e.,* fallopian tubes, ovaries) separately from the uterus. Nine patients showed marked radioactivity in the tubes and ovaries, while in five patients the radioactivity levels were not much higher than the background. In all five of these patients with background levels of radioactivity detected, the authors reported that severe tubal occlusion was confirmed. As the authors discussed: *"**Evidence is available for migration of different substances in either direction within the female reproductive system** between the peritoneal cavity and ovaries via the tubes, uterus and vagina, and the outside. Various living organisms actively follow this pathway in both directions. Gases, fluids, dyes and contrast media can easily be introduced from the vagina into the peritoneal cavity. **If transit can take place so easily, it is probably the same for many chemical substances used for hygienic, cosmetic or medicinal purposes, many of which may have potential carcinogenic or irritating properties**." [**emphasis** added]* This paper provided evidence that migration of talc upwards into the female reproductive tract was considered more than a possibility at this point in time.

48. In a similar study reported in 1985 (McCalley *et al.* 1985), scientists performed a prospective study to evaluate the efficacy of radionuclide hysterosalpingography (RNHSG) using a technique with some modification that had been described by Venter and Iturralde (1979). The authors state: *"As these investigators demonstrated, technetium labeled human albumin microspheres will **normally migrate spontaneously from the vagina to the ovaries**." [**emphasis** added]* This new study confirmed the findings of the 1979 study and showed that if the fallopian tubes are not patent, migration cannot continue. Most importantly, the authors provided the following conclusions: *"Our work confirms the observation of Iturralde and Venter that inert particles are easily and spontaneously transported from the vagina through the genital tract to the ovaries. This implies that sperm motility, although possibly essential, e.g., for penetration of the ovum, may not be the basic factor in sperm transport. **It also confirms that pathogenic materials***

deposited in the vagina can be transported onto the ovary and may play a role in the etiology of some ovarian carcinomas. *[emphasis added]* The scientific studies providing notice on the ability of particles to migrate continued to build.

49. Another source of human data related to migration of substances upwards in the female reproductive tract is found in a book chapter that was prepared from a presentation made at the 7th International Symposium on Controlled release of Bioactive Materials (July 27-30, 1980) (Gardner *et al.* 1981). The chapter provides an overview of what was known at the time regarding movement of particles and other materials up the female reproductive tract from the vagina. The chapter was focused on using that route of exposure as a method for delivery of drugs in women. The author stated: *"The concept of a particulate drug-delivery system is further supported by studies in humans, which* ***demonstrate the movement of inert particles through the reproductive tract****. Following placement in either the vagina, cervix, or uterus, particles such as carmine or carbon black have been observed to* ***migrate into the fallopian tubes or peritoneal cavity****."* *[**emphasis** added]* Additionally, the authors described new studies in Stumptail monkeys. They reported that vaginally delivered drug particles were able to migrate through the cervix into the uterus. They stated: *"Transcervical migration from the vagina to the uterus (24 hours post-insertion) was observed to some degree in six out of eleven animals. In these studies, it appeared that capsule diameters less than 300 microns in diameter showed preferential migration. However, one animal out of three at the largest capsule diameter did show migration of greater than three percent of the inserted microcapsules."* In a study in one baboon, the authors reported that six hours after insertion of two different sizes of tracer microcapsules there was essentially no difference in transcervical migration between the two sizes, and that migration was rapid (within six hours) into the cervix, uterus, and fallopian tubes. These studies provided additional evidence for migration of substances from the vagina upwards into the reproductive tract, including a study in primates.

50. Three additional animal studies appeared in the scientific literature in 1985 and 1986 that are relevant to the issue of talc migration in the female reproductive tract (Wehner *et al.* 1985; Henderson *et al.* 1986; Wehner *et al.* 1986). Henderson and colleagues from the Tenovus Institute reported on the ability of talc to migrate from the vagina to the ovary in rats (Henderson

et al. 1986); this same research group had published data on the finding of talc in the human ovary (Henderson *et al.* 1971; Henderson *et al.* 1979). The authors stated: *"**Direct communication between the external environment and the peritoneal cavity** exists in the female via her genital tract." [**emphasis** added]* The study was undertaken after Henderson and colleagues (1984) showed that injection of talc beneath the bursal sac around the ovary in rats was accompanied by *"associated epithelial changes not inconsistent with the histological picture of premalignancy."* In the first of this new set of experiments by Henderson and colleagues in 1986, eight rats received intra-uterine talc (100 mg/ml suspension; 250 μl volume) injections. Rats in Group I (four rats) were sacrificed five days after talc exposure, and their ovaries were removed. Rats in Group II (four rats) received further talc uterine injections six days or 15 days after initial treatment. On day 20, two rats were sacrificed, and the remaining two rats were sacrificed 22 or 30 days after initial treatment. In all cases, ovaries were removed and analyzed for the presence of talc particles. In a second experiment employing vaginal delivery of talc, twelve rats were divided into two groups of six. Rats in Group I had a 250 μl suspension of talc (100 mg/ml) deposited into their vagina, while rats in Group II received vehicle treatment. Two animals in each group were sacrificed 24 hours, 48 hours and four days after treatment. Their ovaries were removed and processed for detection of talc particles. Particles of talc were identified in the ovaries of all rats at all time points where talc had been instilled into the uterus. With vaginal instillation, talc particles were detected in two of the animals when sacrificed after four days.

51. In the two studies published in 1985 and 1986, Wehner and colleagues (Wehner *et al.* 1985; Wehner *et al.* 1986) investigated the translocation of talc in animals. As noted in the studies, these were commissioned and funded by PCPC.[43] At the time these studies were conducted, Dr. Wehner was also a consultant with Johnson & Johnson. Wehner *et al.* (1985) first examined the ability of bone black particles to translocate from the vagina upwards into the oviducts in monkeys. Five monkeys were instilled with 0.3 ml of a 4% bone black suspension in the posterior fornix during their mid-menstrual cycle, followed by injection of oxytocin intra-muscularly. Animals were sacrificed either one hour (n=3) or 72 hours (n=2) after vaginal instillation was performed. The authors stated that they did not believe any translocation had occurred but could not rule it out with certainty. Thus, two additional monkeys were administered

[43] The PCPC was known at the time as the CTFA (see footnote on page 329 of Wehner *et al.* (1986)).

radiolabeled talc in a pilot study (single doses of talc) and the animals were sacrificed after 72 hours. Again, the authors reported no translocation occurred in the animals. In a follow-up study, Wehner *et al.* (1986) again examined talc migration in monkeys. Unlike the monkey studies of Gardner *et al.* (1981) and the studies in rats and rabbits discussed above, this was the only animal study published up to this time where the authors reported no translocation of talc to the oviducts. Six monkeys were used by Wehner and colleagues in this *in vivo* study where low doses of radiolabeled talc (125 mg) were instilled into the vagina of the monkeys under sedation, 30 times over 45 days. In three of six monkeys tested, there was no talc found and the investigators believed it may have been due to menstrual flow that had occurred in the monkeys at different times during the experiment. The authors also stated that their results differed from those of an earlier group (Gardner *et al.* 1981) and suggested the differences may have been due to use of much lower doses of talc, different materials, and longer sedation times. The data by this group were inconsistent with other animal data but most importantly they were inconsistent with the human data which is the most relevant data in terms of the issue of movement of particles in women.

52. By the 1990's the issue of migration of substances upwards in the female reproductive tract was discussed in the medical literature in review articles, indicative of the general acceptance in the scientific community of the ability of particles to migrate up the female reproductive tract. In a 1994 review, Lauchlan (1994) states that talc can reach the ovaries through a patent vagina and describes the action of genital application of talc powder as a mode for internal exposure to talc particles. In another review (Wright *et al.* 1996), the authors began by stating: *"Dusting powders are used…**These powders can gain access to the abdominal cavity through the vagina** and during surgery, and they have caused numerous complications that have serious, life-threatening consequences." [**emphasis** added]* In the discussion section of this paper the authors pointed out that the known toxicity of talc in human tissue and *"the ability of the female genital tract to transport particles to the abdominal cavity"* should lead to physicians discouraging their patients to use talcum powder in the perineal area or when dusting diaphragms.

53. In a 1996 article, scientists directly addressed the issue of perineal talc usage and ovarian talc particle burden (Heller *et al.* 1996). The scientists examined ovarian tissue from 24 women undergoing ovary removal; the patients were interviewed regarding talc usage. Twelve

women reported frequent perineal talc applications, while twelve reported no use, although diapering history was not available in all women (the authors considered baby powder use during diapering as a potential source of talc powder exposure in the past). The authors conclusions were stated in their abstract as follows: *"The detection of talc in all ovaries demonstrates that it can reach the upper genital tract. Widespread exposure to talc during diapering may contribute to the ubiquitous presence of talc in ovarian tissue."* This paper has been criticized based on the issue of potential laboratory contamination that could have contributed to the results, as well as the fact that women reporting no perineal use had talc detected in ovarian tissue. Regardless of these limitations, however, the results showing higher overall particles counts in women reporting perineal application of talc are nevertheless consistent with the ability of talc particles to migrate up the female reproductive tract. More importantly, this study is but a small piece of the overall evidence that supports the ability of talc to migrate from the vagina to the ovaries.

54. In a series of studies conducted in the 1990's and into the 2000's, Dr. Kunz reported on the importance of the uterine peristaltic pump to the ability of sperm to be rapidly transported through the female reproductive tract (Kunz *et al.* 1996; Kunz *et al.* 1997; Kunz and Leyendecker, 2002; Kunz *et al.* 2007). In the initial studies, Kunz and colleagues (Kunz *et al.* 1996) used hysterosalpingoscintigraphy as a tool to examine transport of particles up the reproductive tract in women. Technetium-labelled albumin spheres from 5 to 40 microns (a size similar to talc particles found in body powders) were instilled at the posterior vaginal fornix (upper vaginal area) and the path of the spheres was followed. The authors reported immediate movement of the spheres up the tract, with spheres detected in the fallopian tubes within minutes. The movement was greatest during the follicular phase of a woman's cycle. The authors stated: *"Furthermore, our studies with inert particles suggest that this directed ascension is not a property of the spermatozoa and is thus not provided by mechanisms such as chemotaxis,* ***but rather constitutes a specific utero-tubal function controlled by the dominant follicle in that the uterine myometrium with its specific architecture (Goerttler, 1930) is activated and contracts in a manner providing this directed transport****." [***emphasis*** *added]* In other words, the motility of the sperm was not needed for transport to occur. In a 2007 study (Kunz *et al.* 2007), Dr. Kunz used methods similar to ones employed in his 1996 study. He again showed that technetium-labelled albumin spheres from 5 to 40 microns (a size similar to talc particles found in body powders) that had been instilled into the

vagina were transported up the female genital tract, both with and without oxytocin use. The paper describes the now well-established ability of small particles to migrate upwards, with greatest movement occurring during the follicular phase of a woman's cycle (see reviews of the role of the uterine peristaltic pump, *e.g.,* Kunz *et al.* 1997; Kunz and Leyendecker, 2002; Zervomanolakis *et al.* 2007).

55. Several additional studies were identified in the scientific literature that related to particle migration in women (Kadanali *et al.* 2001; Sjosten *et al.* 2004; McDonald *et al.* 2019a; McDonald *et al.* 2019b; Johnson *et al.* 2020). Kadanali and colleagues (2001) discussed upwards transport in the genital tract in women. Although the focus of their paper was on movement of sperm in women with IUD devices in place, one group of women were treated by intra-vaginal instillation of albumin microspheres (referencing use of the method of Iturralde and Venter) instead of sperm. The microspheres were from 10 to 90 microns in size (also in the size range of talc particles found in body powders). The authors reported that while active sperm migration was greatly inhibited (9 of 14 subjects, 65%) in the presence of an IUD, passive transport of the particles was not affected (10 of 10 subjects, 100%) in IUD-bearing women. These data provided additional support for the migration of particles upwards into the fallopian tubes of women, even women with an IUD device implanted. With respect to powder migration specifically, Sjösten and colleagues (2004) reported results of a study in humans to confirm migration that had been observed in an animal model. In the study, one group of women (n=12) underwent a gynecological exam with powdered gloves the day before an abdominal hysterectomy and another group was examined with powdered gloves four days before surgery (n=12). Two control groups were examined with powder-free gloves (n=12 or n=14). Cell smears were taken from the peritoneal fluid and during the operation further smears were taken from the fallopian tubes, uterine cavity and cervical canal. The authors reported that retrograde migration of starch particles had occurred in humans after examination with powdered gloves. The authors concluded: *"Consequently, powder or any other potentially harmful substance that can migrate from the vagina should be avoided."* Of the more recent studies, the studies by McDonald and colleagues (2019a, 2019b) addressed the issue of migration of talc in women with ovarian cancer that reported perineal use of talc body powders. The studies aimed to differentiate the presence of talc in pelvic lymph nodes due to talc exposure versus contamination. Considered together these studies showed that talc

particle burden in nodes correlated with perineal usage of talc powder. These studies provide additional support for the ability of talc to translocate from the genital area of women up the reproductive tract. The most recent study (Johnson *et al.* 2020) was discussed by Health Canada in its 2021 talc risk assessment (Health Canada, 2021). The regulators stated with respect to this study:

> *"Some further work was done (Johnson et al. 2020) to compare talc particles from commercially available powders to those found in pelvic tissues taken from 11 randomly selected ovarian cancer patients with a known history of long-term perineal talc use. PLM and SEM/EDX were employed to measure the talc particles, and extensive measures were taken to control for contamination. The talc particles taken from tissues of the patients were most often located within benign tissue, reactive fibroblastic tissue, or chronically inflamed tissue near a tumour, rather than within tumours; the presumption is that talc accumulates in benign tissue some time prior to the tumour developing. The particle size and dimensions of talc particles found in the commercial samples are consistent with those found in the pelvic tissues of the patients: 77.7% of commercial samples and 83.5% of talc from tissues fall within the same ranges for aspect ratio and area. This lends support to the idea that externally-applied talc can migrate from the perineal area."*[44]

56. Considered together, these studies conducted in both humans (*in vivo* and *ex vivo* studies) and in animals demonstrate the ability of particles to be transported upwards against gravity in the female reproductive tract. These studies provide support for the FDA statement in 2014 that the potential for particulates to migrate from the perineum and vagina to the peritoneal cavity *"is indisputable"*, and for Health Canada's conclusions in 2021 that genital talc use poses a potential health risk to humans that will be addressed with new risk mitigation actions.[45] More importantly, studies going as far back as the 1960's provided direct evidence for the potential of particles to migrate from the vagina to the ovaries in humans. At least in 2004, Imerys was acknowledging that *"compelling evidence"* for migration had been published (IMERYS288328-330).

[44] See pages 21-22 of the Canadian 2021 Talc Screening Assessment.
[45] https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/75453a-eng.php

57. Before leaving this discussion of talc migration, it is important to point out that in its review of the issue of talc migration in the genital tract of women, the CIR panel mentions many of the same studies described above; however, there is no mention of eight additional human studies and reviews of the issue (*i.e.,* Parmley and Woodruff, 1974; McCalley *et al.* 1985; Lauchlan, 1994; Wright *et al.* 1996; Kunz *et al.* 1996; Kunz *et al.* 1997, Kadanali *et al.* 2001; Kunz and Leyendecker, 2002; Kunz *et al.* 2007). All eight of these papers were available by the time of the CIR review. Therefore, it appears the CIR panel failed to account for all the studies that informed on the issue of migration of particles, such as talc moving upwards through the reproductive tract. This omission is particularly important given the fact that the CIR panel stated the following with respect to the epidemiological studies and how that data was considered:

> *"The Panel stated that causation would depend on the migration of talc from the perineum to the ovaries. There is no conclusive explanation for the presence of talc in the ovaries reported in some studies. However, the Panel agreed that there is no known physiological mechanism by which talc can plausibly migrate from the perineum to the ovaries." [see page 23 of the CIR Final Report dated April 12, 2013]*

The CIR process (discussed in detail below) was limited by the omission of a series of human studies and scientific review papers directly relevant to the issue of talc particle migration. Based on the totality of the scientific evidence, which includes more than the data available to or even considered by the CIR panel in 2013, I agree with the FDA's conclusions on this issue and assign little weight to the conclusions reached by the CIR panel concerning talc migration. As already discussed above, in the recent talc risk assessment performed by Health Canada with respect to perineal exposure to talc in cosmetic body powders, they concluded that *"there is the potential for perineal exposure to talc from the use of various self-care products"*[46], a finding consistent with the FDA.

VI. Talc and Cancer

58. In this case, the toxicity of concern for talcum powder products exposure in humans is cancer. The specific risk issue for this case is exposure to powdered talc products through perineal or genital application, as well as inhalation exposure, leading to migration of talc internally, resulting in ovarian cancer. The issue of talc and cancer risk in humans has been

[46] See page 43 of the Screening Assessment document

recognized for decades (see papers discussed in reviews such as EPA, 1992; IARC, 2010; IARC, 2012). Although ovarian cancer is the focus of the current case, other forms of cancer have also been linked to talc exposure (*i.e.,* lung cancer with inhalation exposure to talc; IARC, 2010) To determine whether there is a reasonable basis to conclude there may be a health hazard associated with talcum powder products, it is important to review the totality of the evidence to determine whether there is scientific support. Therefore, I have considered available *in vitro* and *in vivo* toxicology data, mechanistic data, epidemiological studies, and other evidence. In reviewing the evidence, I employed the methodology as discussed earlier in my report (*e.g.,* paragraphs 11, 12, and 13).

59. There is a body of mechanistic data that also needs to be considered when looking at the issue of talcum powder products and risks to human health. It is important to remember that administration of even a single dose of talc in animals has been shown to produce adverse effects locally, at the site of exposure, that have included granulomatous reactions, cellular proliferation, and adhesions (as reviewed by EPA, 1992). Thus, evidence shows that talc exposure induces local tissue responses that are adverse effects, not simple adaptive effects, and those effects lead to tissue damage.

60. Talc can induce toxicity in tissues and cells through direct contact. The studies discussed above related to the ability of talc to migrate from the vagina upwards in the reproductive tract in women are important evidence that talc can arrive at sites where local tissue toxicity would be produced, such as the fallopian tubes and the ovaries. Studies looking at local tissue effects of talc would be important when examining a mechanistic basis for talc carcinogenicity in humans. Starting in the 1980's, studies appeared in the scientific literature related to understanding the local tissue effects of talc. In an early study, the cytotoxicity of seven different respirable talc products (expected to be of high purity) provided to researchers by the PCPC were studied (Davies *et al.* 1983). Specifically, the fibrogenic potential of talc was investigated through use of a cell bioassay (macrophage toxicity) using murine peritoneal macrophages. All seven talc samples tested were found to be cytotoxic and the authors stated they *"would be expected to be fibrogenic in vivo"*. In another study (Hamilton *et al.* 1984), direct exposure to what was claimed to be asbestos-free talc (via single intra-bursal injection) on the surface of the ovaries of rats was associated with adverse

effects including *"focal areas of papillary change"* on the surface epithelium of the ovaries, often discussed as pre-neoplastic lesions; thus, talc was toxic to ovarian tissue in mammals. Beck and colleagues (1987) examined the local tissue toxicity of talc dust (stated to be asbestos-free and granite-free dust), as well as other mineral dusts,[47] *in vivo* in animals (hamsters) following a single intra-tracheal instillation of a dust into lung tissue. The experiments examined the dose-response relationship (0.15, 0.75 and 3.75 mg talc/100 g body weight) and the time course (1 to 14 days post-exposure) of the effects of dust exposure in lung tissue. The authors stated: *"One day after exposure, both talc and granite dust resulted in elevated enzyme levels and pulmonary cell numbers in BAL [bronchial alveolar lavage fluid]. Macrophage phagocytosis was also inhibited. Based on results from earlier studies, response levels were either intermediate between nontoxic iron oxide and toxic a-quartz or comparable with n-quartz. The response to granite dust diminished fairly rapidly over time. By contrast, after talc exposure, there was a more persistent elevation in enzyme levels, and macrophage phagocytosis remained depressed. These results indicate that when a similar mass was deposited in the lungs,* ***talc caused more lung injury than did granite****." [****emphasis*** *added]* In another study (Radic *et al.* 1988), talc was shown to suppress immune system function in rats injected subcutaneously with talc. Talc induced granulomatous reactions in the animals, and spleen cells from talc-treated rats suppressed the immune response. Each of these studies provided evidence that talc is toxic to cells and tissues that are contacted with talc dusts/particles, including ovarian tissue.

61. In 1993, the results of chronic GLP-quality studies conducted from 1984-1986 in rats and mice were reported (NTP, 1993; P-0832 was the draft report). In these studies, using standard study methods of the time, the potential for talc (stated to be asbestos-free) to produce cancer following inhalation was studied. The study rationale was stated as follows: *"Talc was nominated by NIOSH in 1978 for testing by NTP because of the paucity of adequate information on its carcinogenicity and because of widespread human exposure. The inhalation route was chosen because it is the most common route for human exposure."* Although earlier studies had investigated the cancer potential of talc (see review in IARC, 1987), limitations in study design affected their utility for human health risk assessment (*i.e.,* less than lifetime exposures, small group sizes, *etc.*). An important feature of this study was the interim sacrifices performed in both

[47] Granite dust was tested in this study as well.

rats and mice in all three exposure groups of both sexes (see Table 5 and Table 11 of NTP, 1993). This meant that the evolution of lung lesions was examined in the animals, allowing for identification of a potential mechanism for lesions that developed in lung tissue. The study authors concluded:

> *"Under the conditions of these inhalation studies, there was some evidence of carcinogenic activity of talc in male F344/N rats based on an increased incidence of benign or malignant pheochromocytomas of the adrenal gland. There was clear evidence of carcinogenic activity of talc in female F344/N rats based on increased incidences of alveolar bronchiolar adenomas and carcinomas of the lung and benign or malignant pheochromocytomas of the adrenal gland."*

This information alone is significant for human health risk assessment; however, the findings from the interim sacrifices in both rats and mice were extremely useful in terms of identifying a mechanism for lung tumors in rats and mice. The text from the study is quoted below as it provides important support for a mechanism for talc-induced carcinogenesis.

> *"Although the inflammatory response was basically similar in rats and mice, there were important species differences. The lesions in rats were generally more extensive and more severe than those in mice at similar exposure concentrations. In rats, foreign body giant cells were occasionally observed and some of the alveolar macrophages developed the morphological characteristics of epithelioid macrophages. More importantly, the* ***inflammatory lesions in rats were accompanied by interstitial fibrosis, hyperplasia of alveolar type I1 epithelial cells, and, infrequently, squamous metaplasia of the alveolar epithelium****." [****emphasis*** *added; see page 51 of NTP 1993]*
>
> *"A* ***potential mechanism*** *for the development of pulmonary neoplasms associated with insoluble particulate substances is that* ***the prolonged stimulus for cell replication, due not only to cell injury but to the release of mitogenic growth factors from alveolar macrophages, provides a favorable environment for the promotion and progression of spontaneously initiated cells.*** *The interim evaluations in the NTP talc study clearly demonstrate* ***a progressive impairment of homeostatic growth regulation in the areas of chronic inflammation and fibrosis associated with talc deposition in rats****. Hyperplasia of the alveolar epithelium was evident at 6 months and became more extensive and severe*

*with duration of exposure. Not only were there increased numbers of cells (hyperplasia), but some cells assumed morphologic features atypical of regenerating or differentiated type I1 cells (epithelial dysplasia). The altered or dysplastic epithelium was particularly evident in areas of fibrosis. The squamous metaplasia observed in female rats also represents altered differentiation of populations of alveolar epithelial cells and is notable in light of the development of squamous cysts and squamous cell carcinomas." [**emphasis** added; see pages 54-55 of NTP, 1993]*

Thus, these data from interim sacrifices in rats and mice provided an important signal for human safety. The 1993 NTP study has been criticized and conclusions reached by the original authors have been questioned (*i.e.,* Carr, 1995; CIR, 2013). Yet, even with its limitations, the study provides important information on talc toxicity that is relevant to assessing the risks of cancer in humans. In fact, scientists that initially reviewed the study supported the use of the data for listing of talc in NTP's Report on Carcinogens (RoC; discussed in more detail below). It also should be noted that based on an inhalation route of exposure in rats and mice that was employed in the studies (NTP, 1993), the studies would not be expected to produce ovarian tumors in rats or mice given the route of exposure that would severely limit any perineal exposure to talc. Moreover, unlike humans, the ovaries of rats and mice are completely covered by a bursal sac, making direct access to ovarian tissue unlikely when exposure is assumed to be due to vaginal penetration and migration to the ovaries.

62. In more recent studies, the biologic basis of effects in cells and tissues associated with exposure to talc that could be linked to carcinogenesis were evaluated. In one study, (Buz'Zard and Lau, 2007) normal ovarian cells in culture were treated with increasing concentrations of talc in solution, either with or without the presence of a chemotherapeutic agent that has been shown to have anti-cancer activity (*i.e.,* inhibits oxidative damage in cells, induces apoptosis of cancer cells). The authors reported that talc treatment increased generation of reactive oxygen species in ovarian cells and induced neoplastic transformation. In another study looking at cellular changes associated with mineral exposure, Shukla and colleagues (2009) examined mineral pathogenicity of four different particles, including asbestos and non-fibrous talc. Human lung mesothelial cells and human ovarian epithelial cells in culture were employed. Both types of cells were exposed to increasing concentrations of asbestos, talc, titanium oxide and glass beads.

The asbestos was identified as crocidolite asbestos with a mean size of 7.4 µm and had greater than 3:1 length to width ratio. The talc was stated to have a mean size of 1.1 µm and was stated to occur as *"platy particles that were uniform in appearance"* (by field emission scanning electron microscopy). The results of most interest in terms of mechanism of action that relates to the potential to produce a carcinogenic response in tissue included the cell viability data and the changes in gene expression induced by exposure to asbestos and talc. As expected, asbestos fibers were toxic to human cells, both lung and ovarian cells; asbestos is a known human carcinogen. The authors reported that the lung cells were more sensitive to the toxic effects of asbestos; however, testing of only two doses of asbestos limit the conclusions that can be drawn about differences between cells. In the case of talc, lung cell viability was decreased in a dose-dependent manner; decreased viability was reported at talc doses of 15 and 20 $\mu g/m^2$. When two lower doses of talc, 1 and 5 $\mu g/m^2$, were tested in ovarian cells, there was no effect on cell viability. Gene expression changes in lung mesothelial cells also were examined, and exposure to asbestos for up to 24 hours was associated with significant effects on gene expression. The authors reported that fewer gene expression changes occurred in ovarian cells exposed to asbestos. They also reported that fewer gene expression changes were observed in lung cells following exposure to talc at a dose of less than 5 $\mu g/m^2$ for up to 8 hours, and no significant changes in ovarian cell gene expression were observed with talc exposure. However, when the list of genes whose expression was affected by asbestos and talc was examined, it is seen that some of the genes affected are involved in cellular processes that relate to oxidative stress and inflammation. The authors of this study failed to test talc with the same rigor that asbestos was tested in their study, limiting the data collected on talc itself. Nevertheless, the study did reveal statistically significant increases in *ATF3* and IL8 expression by asbestos and non-fibrous talc at certain concentrations. The data collected with asbestos exposure supports known toxicity of induction of oxidative stress as a mechanism underlying carcinogenesis (IARC, 2012). In a more recent study examining the biologic basis of effects in cells and tissues associated with exposure to talc that could be linked to carcinogenesis, Mandarino and colleagues (2020) focused on the effect of talc exposure on immunosurveillance and the activity of macrophages in a high estrogen environment; in addition to the release of tissue-damaging factors from macrophages, these cells could have compromised immunosurveillance activity that results in decreased tumoricidal activity. The authors stated:

"We found that murine ovarian surface epithelial cells (MOSEC), a prototype of certain forms of ovarian cancer, were present in larger numbers after co-culture with macrophages treated to a combination of talc and estradiol than to either agent alone or vehicle. Control particles (titanium dioxide, concentrated urban air particulates or diesel exhaust particles) did not have this effect. Co-exposure of macrophages to talc and estradiol has led to increased production of reactive oxygen species and changes in expression of macrophage genes pertinent in cancer development and immunosurveillance. These findings suggest that in vitro exposure to talc, particularly in a high-estrogen environment, may compromise immunosurveillance functions of macrophages and prompt further studies to elucidate this mechanism."

63. The same research group (Hillegass *et al.* 2010) further examined the pathogenicity of asbestos as compared to other particles, including talc. The authors reported that their analysis of microarray data confirmed that lung cells were *"more responsive than ovarian cells to crocidolite asbestos or non-fibrous talc, and that crocidolite asbestos elicited greater responses in both cell types when compared to non-fibrous talc"*. As before, however, the group failed to test talc across a range of doses that would be necessary to examine its effects in these assays, using only doses that were equivalent to asbestos even though it was known that the crocidolite asbestos would be expected to be more potent in terms of biological reactivity than talc. The authors did, however, report that *"the pathogenesis of asbestos-associated diseases is most commonly associated with a persistent inflammatory response initiated by ROS, growth factors, and/ or various pro-inflammatory factors such as cytokines or chemokines"*. Therefore, this paper provided further evidence supporting the mechanism of inflammation and generation of reactive oxygen species as important to the tissue responses induced with exposure to particles that would include both asbestos and talc.

64. In a more recent study (Shim *et al.* 2015), the effect of talc to induce oxidative stress *in vivo* following administration of talc was examined. Rats were exposed to talc via whole-body inhalation at concentrations of 0, 5, 50 and 100 mg/m^3, six hours per day, five days per week, for four weeks. It should be remembered that in a GLP-quality lifetime study in rodents (NTP, 1993), rats were exposed to talc via whole-body inhalation at doses of 0, 6 and 18 mg/m^3, six hours

per day, five days per week, and there was clear evidence of talc-induced chronic inflammation, reparative processes and cellular proliferation (as evidenced by lung pathological changes observed at interim sacrifices of 6, 11, and 18 months). This shorter-term study in rats by Shim *et al.* (2015) focused on understanding the role of oxidative stress in the tissue responses to talc, a general mechanism that has been linked to chronic inflammation and cancer, including ovarian cancer (*e.g.,* Saed *et al.* 2017; Saed *et al.* 2018; Fernandes *et al.* 2015; Landskron *et al.* 2014; Kamp *et al.* 2011; Grivennikov *et al.* 2010; Lu *et al.* 2006; Rakoff-Nahoum, 2006; Senthil *et al.* 2004; Ness *et al.* 2000; Savant *et al.* 2018; Ding *et al.* 2021). Shim and colleagues (2015) reported that inhalation of talc for four weeks was associated with macrophage aggregation and oxidative damage in the lung, including significantly increased expression of superoxide dismutase 2 (SOD 2), a biological indicator of oxidative damage.

65. In several references authored by the same research group, the effects of talc exposure to induce oxidative stress in ovarian cancer cells have been investigated and described (Fletcher *et al.* 2018; Fletcher and Saed, 2018; Fletcher *et al.* 2019). The first reference describes a presentation at a scientific meeting in March of 2018; the researchers reported on the ability of talc to affect markers of oxidative stress in ovarian cancer cells in culture (Fletcher *et al.* 2018). Both normal ovarian epithelial cells and cancerous ovarian epithelial cells were incubated with talc at concentrations of 0, 200 and 500 µg/ml for 24, 48 and 72 hours. The talc was purchased from Sigma Aldrich.[48] There was a marked increase in mRNA levels of pro-oxidant enzymes in both ovarian cell lines as compared to controls (untreated), and a marked decrease in mRNA levels of anti-oxidant enzymes in both cell lines as compared to controls (untreated cells). These changes, indicative of a pro-oxidant state in the cells (oxidative stress), were reported to occur as early as 24 hours after exposure. The authors concluded: *"This is the first report to show that talcum powder induces biological effect by further enhancing the redox state in both normal ovarian epithelial cells as well as ovarian cancer cells. The results of this study will provide a molecular basis to previous reports that link genital use of talcum powder to increased risk of epithelial ovarian cancer."* In the second presentation in 2018 by this same laboratory (Fletcher and Saed, 2018), additional investigation of the effects of talcum powder on ovarian cancer cells was discussed. The objective of the studies performed was to determine the effects of talcum powder

[48] The Sigma Aldrich website indicates that the talc sold is pharmaceutical grade talc.

on levels of the cancer antigen, CA-125, in both normal ovarian cells and ovarian cancer cells. The authors stated that levels of CA-125 are elevated in more than 80% of women with advanced ovarian cancer and 50% of women with early-stage cancers. Ovarian cells were exposed to 0 or 1000 µg/ml talc for 72 hours and levels of CA-125 were determined by ELISA methods. The authors reported that there were increases in CA-125 levels in response to talc treatment in both normal and cancerous cells. The authors concluded: *"Talcum powder induces a biological effect by further enhancing CA-125 levels in ovarian cancer cells as well as in normal ovarian epithelial cells. This will provide a molecular basis to previous reports that link genital use of talcum powder to increased risk of epithelial cancer."* The 2019 publication with the same authors (Fletcher *et al.* 2019) is a peer-reviewed paper describing the 2018 studies[49] related to the effects of talc on the expression of key redox enzymes, CA-125 levels, and cell proliferation and apoptosis in normal and ovarian cancer cells. The authors stated: *"These findings are the first to confirm the cellular effect of talc and provide a molecular mechanism to previous reports linking genital use to increased ovarian cancer risk."* In a review of the pathogenesis of ovarian cancer by Dr. Saed and colleagues (Saed *et al.* 2018), the importance of oxidative stress to pathogenesis and prognosis of ovarian cancer is discussed. Thus, the effects of talc in cells and tissues that are linked to oxidative stress provide additional insight into the molecular basis of talc-induced ovarian cancer in humans.

66. Talc body powders manufactured and sold by Imerys and Johnson & Johnson were a mixture of compounds, many of which have toxic properties. There is consistent evidence linking talc as well as the other components of talc with initiation of inflammation at the local site of exposure (discussed above), as well as evidence that talc induces biologic effects that result in pre-cancerous lesions (NTP, 1993). Inflammation is a well-studied mechanism of carcinogenesis (*e.g.,* Fernandes *et al.* 2015; Grivvennikov *et al.* 2010; Fleming *et al.* 2006; Lu *et al.* 2006; Rakoff-Nahoum, S. 2006; Ness and Cottreau, 1999). As discussed in a recent review of the topic of inflammation and cancer (Grivennikov *et al*. 2010), there are several basic facts about inflammation and cancer that include the following: (1) chronic inflammation increases cancer risk; (2) subclinical, often undetectable inflammation may be as important in increasing cancer risk; (3) various types of immune and inflammatory cells are frequently present within tumors; (4)

[49] It is common for scientists to first publish their findings in the form of an abstract or presentation for a scientific meeting and then follow with a full paper that is published in the peer-reviewed literature.

immune cells affect malignant cells through production of cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species; (5) inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression; (6) in developing tumors anti-tumorigenic and pro-tumorigenic immune and inflammatory mechanisms coexist, but if the tumor is not rejected, the pro-tumorigenic effect dominates; (7) signaling pathways that mediate the pro-tumorigenic effects of inflammation are often subject to a feed-forward loop; and (8) certain immune and inflammatory components may be dispensable during one stage of tumorigenesis but absolutely critical in another stage. Therefore, in the case of talc, even if tissue samples from ovarian tumors fail to exhibit signs of active chronic inflammation, an inflammatory role for talc is not ruled out. Instead, the role of talc in inducing the tumorigenic response could be linked to earlier stages of cancer progression.

67. With respect to inflammation and ovarian cancer specifically, a recent prospective epidemiological study performed by investigators at the National Institutes of Health has linked specific pro-inflammatory markers in blood with the presence of ovarian cancer in women (Trabert *et al.* 2014); the authors suggest that these pro-inflammatory mechanisms may be linked to the increased risk of ovarian cancer seen in women exposed to compounds such as talc and asbestos. Other supporting evidence for a link of inflammation with carcinogenesis following talc exposure in women are the studies that have shown that talc exposure can induce oxidative stress in cells (discussed above). Therefore, there are multiple plausible mechanisms that may be related to the cancer hazard posed by perineal talc body powder exposure in women. Additionally, the fact that talc can act as a cancer promoter is also relevant (Stenback *et al.* 1986). Finally, it is important to note that the link of talc with inflammatory processes is an underlying toxic insult that can lead to cancer. This mechanism is consistent with mechanisms linked to other particles that induce cancer (*i.e.,* asbestos and silica; Moller *et al.* 2010, Moller *et al*. 2013; IARC, 1987; IARC, 2010; IARC, 2012). It is also important to realize that there is latency associated with cancer pathogenesis which would also apply in the case of talc.

68. When considered together, the scientific literature on the biological effects of talc, as well as asbestos and other constituents routinely found in talc (discussed above), provide sufficient evidence to show that these chemicals produce cellular changes that have been linked to

carcinogenesis and that the biological mechanism for carcinogenesis (ovarian and/or lung) following exposure to talcum powder products likely involves induction of a chronic inflammatory response. A review of the IARC monographs for talcum powder product constituents, such as asbestiform talc and non-asbestiform talc, nickel, cobalt, and chromium, reveals similarities in the biological effects that are discussed as underlying the carcinogenic potential of the individual compounds. Moreover, available evidence indicates that local exposure to talc particles is likely involved, where "local exposure" means exposure at or near the site of injury, in this case exposure of the ovary and ovarian cancer. It is important to realize as well that in the case of almost any human drug used to treat a disease or symptoms of some condition, the exact molecular mechanism by which the drug produces its effects also are not known. Thus, not knowing every detail about the molecular mechanism underlying talcum powder products and carcinogenesis does not mean that the available data fail to provide support for a likely mechanism. In fact, we know some important things about talc, information that supports the biologic plausibility of the relationship between talc exposure and human cancer. This mechanistic data provides highly plausible biological support for the signal for human cancer risk identified from the epidemiological (discussed below) and animal data.

69. When considered together with general principles of toxicology, the available data relating to mechanism of carcinogenicity of talcum powder products, where the body powders are a mixture of compounds with carcinogenic hazard, indicate that the various compounds in talcum powder products would be expected to produce at least an additive effect on the risk of cancer based on their ability to induce similar biological responses that underly carcinogenesis (Eaton, D.L. and S.G. Gilbert. 2013. Principles of toxicology. In: *Casarett & Doull's Toxicology: The Basic Science of Poisons, 8th edition*. Klaassen, C.D. (ed.). McGraw-Hill: New York: NY. Chapter 2, pp. 19-20; EPA, 2000). The likely mechanism for cancer is related to the similar cellular events that have been linked to carcinogenesis in the case of the known components of talcum powder products.

70. It is well-established that there are two types of chemical carcinogens: genotoxic and non-genotoxic (Klaunig, 2013). A genotoxic carcinogen is one that is mutagenic, may be a complete carcinogen, produces tumors that exhibit a dose-response relationship with exposure,

and for which there is no threshold for cancer initiation[50]. A non-genotoxic carcinogen is one that is not a direct mutagen, exhibits a threshold for tumor development, produces tumors that exhibit a dose-response relationship with exposure, may only function as a tumor promoter, does not directly damage DNA, and may exhibit species, strain and tissue specificity in response. The available evidence indicates that talc may be a non-genotoxic carcinogen, as defined here, based on the evidence showing that it is not genotoxic (in most assays), requires repeated dosing of sufficient duration for tumors to be produced, has been shown to exhibit activity as a tumor promoter for known carcinogens (*i.e.,* benzo(a)pyrene; Stenback *et al.* 1986), exhibits species and tissue specificity in tumor responses (associated with local site of exposure), and has not been shown to directly damage DNA. The available animal cancer data has not been assessed for a threshold for tumor development, but the NTP study data did indicate that the tumor response was a high dose effect. Human studies, however, have indicated that ovarian cancer exhibits a dose-response in terms of being associated with an increased duration of use and frequency of use of talc-based products (*e.g.,* Cramer *et al.* 1999; Terry *et al.* 2013; Wu *et al.* 2015; Schildkraut *et al.* 2016; Berge *et al.* 2018; Penninkilampi and Eslick 2018). Therefore, the available evidence indicates that talc's plausible mechanism of action to induce cancer would be through non-genotoxic (indirect) pathways.

71. I also would like to point out that talc powder is used clinically to cause an acute inflammatory response in a procedure known as pleurodesis. This procedure is designed to cause the two layers of the lung pleura, parietal and visceral layers, to stick together so that the space between the layers is filled with scar tissue. Typically, only a few ounces of fluid would be found between the parietal and visceral pleural membranes, but the fluid can build up to as much as a few liters and is known as a pleural effusion. Both mechanical and chemical means are used to initiate the lung scarring that is needed to treat these effusions. In the case of chemical pleurodesis, a substance such as talc powder can be placed into the chest cavity near the lungs to produce an acute inflammatory response that leads to scarring. The size of the talc particles used in the procedure are important; severe inflammatory effects were more likely when a talc powder with smaller particles, about 50% less than 10 µm, was employed (Arellano-Orden *et al.* 2013). It is

[50] Asbestos has been identified as a genotoxic carcinogen.
(https://www.atsdr.cdc.gov/csem/asbestos/how_does_asbestos_induce_pathogenic_changes.html).

important to note that typical talcum powder products, including those manufactured and sold by Imerys and Johnson & Johnson, contain mostly small particles, less than 10 µm (Zazenski *et al.* 1995; JNJ000326966; IMERYS095244; IMERYS120564-565). Thus, the pleurodesis literature provide further support for inflammation as a known tissue response to talc, even though the type of inflammatory response produced in pleurodesis procedures is acute, not a chronic response as is characteristic of carcinogenesis.

72. As discussed above in paragraph 33, an increased human cancer risk has been linked to components of talcum powder products, such as asbestos. By the 1930's, evidence was available linking asbestos exposure with lung disease, including lung cancer; by the mid 1950's, the majority of scientists believed that asbestos could cause lung cancer, and likely other forms of cancer, in humans (Doll, 1955); and by the 1960's, evidence had accumulated linking asbestos exposure with ovarian cancer, with some studies reporting an increased incidence in women exposed to asbestos. Beginning in the 1970's, the issue of ovarian cancer in women began to be discussed with respect to talcum powder product exposure (Henderson *et al.* 1971; Henderson *et al.* 1979). Since that time, the study of, evidence for, and discussion of, a cause and effect relationship between talc exposure and human ovarian cancer risk has continued to develop in light of the totality of the data (*e.g.,* Cramer *et al*. 1982; Hartge *et al.* 1983; Natow, 1986; Whittemore *et al.* 1988; Booth *et al.* 1989; Harlow and Weiss, 1989; Harlow *et al.* 1992; Chen *et al.* 1992; Rosenblatt *et al.* 1992; Tzonou *et al*. 1993; Cramer and Xu, 1995; Purdie *et al.* 1995; Shushan *et al.* 1996; Chang and Risch, 1997; Cook *et al.* 1997; Green *et al*. 1997; Daly and Obrams, 1998; Eltabbakh *et al*. 1998; Godard *et al.* 1998; Cramer, 1999; Wong *et al.* 1999; Ness *et al.* 2000; Langseth and Kjaerheim, 2004; Mills *et al*. 2004; Jordan *et al.* 2007; Merritt *et al.* 2008; Wu *et al.* 2009; Rosenblatt *et al.* 2011; Kurta *et al*. 2012; Terry *et al.* 2013; Houghton *et al.* 2014; Wu *et al.* 2015; Schildkraut *et al.* 2016; Berge *et al.* 2018; Penninkilampi and Eslick, 2018; Taher *et al.* 2020; O'Brien *et al.* 2020; Davis *et al.* 2021; Woolen *et al.* 2022; Phung *et al.* 2022; O'Brien *et al.* 2024). A review of these studies as a whole shows that exposure to talc by routine genital application is reported to increase the risk of ovarian cancer in women by about 30% (*e.g.,* Cramer *et al.* 1982; Whittemore *et al.* 1988; Booth *et al*. 1989; Harlow and Weiss, 1989; Harlow *et al.* 1992; Rosenblatt *et al*. 1992; Purdie *et al*. 1995; Shushan *et al.* 1996; Chang and Risch, 1997; Cook *et al.* 1997; Cramer *et al.* 1999; Gertig *et al.* 2000; Ness *et al.* 2000; Mills *et al.* 2004; Merritt

et al. 2008; Wu *et al.* 2009; Rosenblatt *et al.* 2011; Kurta *et al*. 2012; Terry *et al.* 2013; Schildkraut *et al.* 2016; Berge *et al.* 2018; Penninkilampi and Eslick, 2018; Davis *et al.* 2021;Woolen *et al.* 2022; O'Brien *et al.* 2024). Not all studies identified in the published scientific literature have reported a statistically significant increased risk of ovarian cancer following talc exposure in women (*e.g.*, Hartge *et al.,* 1983; Chen *et al.* 1992; Tzonou *et al.* 1993; Godard *et al.* 1998; Wong *et al.* 1999; Langseth and Kjaerheim, 2004; Houghton *et al.* 2014; O'Brien *et al.* 2020). With such a large group of epidemiological studies, with varying designs, sizes of the populations studied, and varying measures of exposure, it is not surprising that there are studies that show both an increase in risk as well as those that failed to report such results. Yet, in the large group of studies (more than 25 studies) reporting statistically significant findings, the increased risk is consistently seen to be in the range of 30%. Even in the studies that reported non-statistically significant findings, there often was a trend towards an increased risk in women who used talcum powder products. As recent as 2020, statistically significant findings regarding the association between genital use of talc powder and risk of ovarian cancer were published after analysis of pooled data results from four cohort studies. The paper included a subgroup analysis of the data that focused on women with patent reproductive tracts (O'Brien *et al.* 2020). In response to comments made to Dr. O'Brien regarding her findings she responds as follows:

> *"We completely agree with Dr. Harlow and colleagues that our results, particularly the analyses limited to women with intact reproductive tracts, should not be discounted because of a lack of statistical significance. For all estimates, we reported 95% Cis so readers could consider size and precision. The qualifier that there was no statistically significant association between ever genital powder use and ovarian cancer is a factual report of a test of the null hypothesis; we never equated the lack of statistical significance to evidence of no association.*
>
> *We conducted subgroup analyses with an a priori hypothesis that intact reproductive tracts are required to be susceptible to the exposure. Therefore, even though we stated that findings from subgroup analyses should be interpreted as exploratory, we do not consider them all equally important and agree that the positive association among women with patent reproductive tracts (HR 1.13; 95% CI 1.10-1.26) is consistent with the hypothesis that there is an association between genital powder use and ovarian cancer."*

In their most recent work, O'Brien and colleagues (2024) have reported results of an assessment of recall bias in the prospective cohort study known as the "Sister Study" and found that *"although results show how differential recall would upwardly bias estimates, corrected results support a positive association between use of intimate care products, including genital talc, and ovarian cancer."* In a recent meta-analysis and systematic review of eleven different studies (Woolen *et al.* 2022), the authors reported a statistically significant increased risk of ovarian cancer associated with frequent perineal powder use by women (31% to 65% increased risk). Based on the totality of the data, which includes human epidemiological data related to talcum powder product use and cancer risk in women that is considered in conjunction with the biological data on talc migration, as well as cellular and animal data regarding inflammation and talc's induction of carcinogenicity, the weight-of-the-evidence supports the conclusion that use of talcum powder products may pose a health hazard to women.

73. As a part of my risk assessment, I also considered whether there is a dose response. In the current case where the chemical of concern is a particle, and the route of exposure of concern is external application of a powder that then migrates internally, and the powder itself is a mixture of a variety of compounds some of which are known human carcinogens, the concept of dose is more complex. The human studies do not provide a measure of a single dose in terms that are typical of the cellular (*in vitro*) or animal studies, *i.e.,* mg talc per kg body weight, or mg talc per m^3 inhaled air, or mg talc per ml of solution. In the case of the talc database, dose for human is expressed terms of frequency and duration of exposure. It is a general principle of pharmacology and toxicology that just as the likelihood of a response increases with dose, the likelihood of a response increases with longer term use, and more frequent use (Eaton and Gilbert, 2013). The available *in vitro* and animal study data show that there is a dose-response relationship for talc toxicity (*e.g.,* EPA, 1992; NTP, 1993; IARC, 2010; Buz'Zard and Lau, 2007; Shukla *et al.* 2009; Shim *et al.* 2015). The animal cancer data, when considered in conjunction with the cellular data, indicate that talc is a carcinogen and there likely is a dose-response threshold for tumor development in rodents (NTP, 1993). There are several human studies that provide evidence of a

dose-response relationship[51] for talc exposure and ovarian cancer in women (*e.g.,* Cramer *et al.* 1999; Terry *et al.* 2013; Schildkraut *et al.* 2016; Cramer *et al.* 2016; Berge *et al.* 2018; Penninkilampi and Eslick, 2018; Woolen *et al.* 2022; O'Brien *et al.* 2024). Therefore, there are sufficient scientific data supporting the existence of a dose-response relationship for genital talc use and an increased risk of ovarian cancer.

74. In 1978, the U.S. Congress amended Section 301(b)(4) of the Public Health Service Act, to require the Secretary of the Department of Health and Human Services (DHHS) to publish an annual report that contains a list of all substances that *"are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and to which a significant number of persons residing in the United States are exposed"*.[52] The process of producing the list, known as the Report on Carcinogens, or RoC, results from periodic meetings and is a process managed by the NTP on behalf of DHHS. There have been 15 RoC processes to date, the 15th RoC being published in 2021.[53] Talc was considered as part of the 10th and 12th RoC processes. The 10th RoC meeting where talc was discussed was held in 2000, while the 12th RoC meeting on talc was held in 2005. The 10th RoC deferred action to list talc as a carcinogen, citing a need for additional information; the 12th RoC also deferred action to list talc. It is important to note that the NTP RoC nominated talc for consideration for listing in the 10th RoC based on a review of the available data by a body of scientists without input from industry, and without any direct interaction with other industry groups or representatives with a conflict of interest, consistent with the procedures set forth by IARC (IARC, 2006). Johnson & Johnson, Imerys, and PCPC influenced the 10th RoC process as I discuss later in paragraph 96. It is also important to note that a review of the minutes of the 10th RoC indicates that even though the only public comments made to the panel were from industry representatives, many of the reviewers supported listing non-asbestiform talc as reasonably anticipated to be a human carcinogen (IMERYS 039060 through 085).

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[51] Given the nature of talc as particles and fibers that cannot be metabolized in the body and remain in tissues where they deposit, duration and frequency of exposure are appropriate surrogates for assessing the dose-response relationship between talc use and an increased risk of cancer in human epidemiological studies.
[52] https://ntp.niehs.nih.gov/pubhealth/roc/history/index.htm
[53] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc

75. In 2010, the International Agency for Research on Cancer (IARC) Working Group published its assessment of the carcinogenic potential of non-asbestiform talc. The review of talc had occurred in 2006 and included only those papers available up to 2006. In its 2012 statements about cancer and fibers of the type that are known to occur in talc (IARC, 2012), IARC pointed out that conclusions about asbestos and carcinogenic risk applied to six types of fibers, including *"talc containing asbestiform fibres"* (see page 219 in IARC, 2012). It is important to note here that the IARC review process is not open for public comment and all conclusions reflect the consensus decisions made by global experts in their field and without influence from industry. Additionally, this review occurred after the NTP talc reviews had been completed. Unlike the NTP RoC reviews, the IARC panel was able to reach a consensus regarding the cancer risks posed by talc. The IARC panel concluded that perineal use of non-asbestiform talcum powder products was *"possibly carcinogenic to humans"* (a Group 2B classification) and inhalation of non-asbestiform talc was *"not classifiable as to its carcinogenicity"* (a Group 3 classification). This finding provided additional evidence for the weight-of-the evidence assessment I performed. It should be noted that the 2006 IARC panel did not have access to studies performed after 2006 which include but are not limited to Langseth *et al.* (2008), Terry *et al.* (2013), Wu *et al.* (2009 and 2015), Schildkraut *et al.* (2016), Cramer *et al.* (2016), Berge *et al.* (2018), Penninkilampi and Eslick (2018), Taher *et al.* 2019, O'Brien *et al.* (2020), Health Canada (2021), Davis *et al.* 2021; Phung *et al.* (2022); Woolen *et al.* (2022), and O'Brien *et al.* (2024).[54] These additional studies and/or analyses provide further evidence of the link of talc exposure in women and an increased risk of ovarian cancer. Langseth *et al.* (2008) points to the need for additional study of the relationship between talc use and ovarian cancer as the studies available as of 2008 indicated that use of cosmetic talc in the perineal area may be associated with ovarian cancer risk. Terry *et al.* (2013) performed one of the largest meta-analyses with the talc database. The authors reported that genital use of talcum powder products significantly increased the risk of all types of ovarian cancer. The paper by Schildkraut *et al.* (2016) provided support for the existence of a dose-response relationship between talc use and increased risk of ovarian cancer in women. The papers by Wu and colleagues (2009 and 2015) describe population-based case-control studies of the relationship of ovarian cancer risk to exposures that included use of talc; in both papers the authors reported a statistically significant association between talc use and ovarian cancer. Schildkraut and colleagues

[54] See also paragraph 72.

(2016) reported results from a case-control study where there was a statistically significant increase in risk of epithelial ovarian cancer linked to use of talc body powders, including genital talc use, with duration and frequency of use being important. Cramer *et al.* (2016) reported results from a retrospective case-control study of talc use and the risk of ovarian cancer; the authors reported there was a statistically significant increased risk of ovarian cancer with talc use and the trend increased with longer-term use. Berge *et al.* (2018) reported a statistically significant increased risk of serous carcinoma of the ovary, as well as the identification of a dose-response relationship (increased duration of use). Penninkilampi and Eslick (2018) performed another meta-analysis of the studies in women exposed to talc through perineal dusting with talc body powders and reported that *"there is a consistent association between perineal talc use and ovarian cancer"*. Taher *et al.* (2019) reviewed the available scientific literature studies on the epidemiology of talc and ovarian cancer risk and concluded that perineal talc use is a possible cause of ovarian cancer. O'Brien *et al.* (2020) performed a pooled analysis of available prospective cohort studies and found that in the subgroup of women who reported ever use of talc powder in the genital area and had a patent reproductive tract, there was a statistically significant increased risk of ovarian cancer. Health Canada's talc screening assessment was reported in final form in April of 2021; it was stated in the report that: *"With regards to perineal exposure, analyses of the available human studies in the peer-reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. The available data are indicative of a causal effect."* Davis *et al.* (2021) was a pooled analysis including the largest number of African American cancer cases. The authors reported a statistically significant increased risk of ovarian cancer in women (African American and White) that had used talc-based body powders. The recent meta-analysis by Woolen and colleagues (2022) also included a large number of ovarian cancer cases and focused on frequent (at least two times per week) perineal use of talc body powders and ovarian cancer; they reported a statistically significant increased risk of ovarian cancer in women that were frequent users of talc products. Additionally, Phung and colleagues (2022) evaluated the effect of genital talcum powder use in women with and without endometriosis and reported that the risk of ovarian cancer was increased in women that reported genital use of talc-based body powder. They also reported that the risk of ovarian cancer was higher in women with endometriosis who applied talcum body powder to their genitals. Finally, as already mentioned above, O'Brien and colleagues' analysis of recall bias in the prospective cohort study known as the Sister Study

(O'Brien *et al.* 2024) also found that results *"support a positive association between use of intimate care products, including genital talc, and ovarian cancer."* These additional studies and evaluations add to the weight of evidence that genital use of talcum powder products may be a health hazard.

76. Therefore, the weight-of-the-evidence indicates that genital exposure to talcum powder products increases the risk of ovarian cancer in women. This conclusion is supported by data that includes, but is not limited to the following: (1) the known toxic effects of talc and the other components of talcum powder products; (2) studies that have identified the biologically plausible mechanisms for cancer in humans; (3) the likelihood that talc particles can reach the ovaries; (4) the existence of a dose-response relationship for toxicity including the risk of cancer; and (5) the large human database that includes studies conducted over a period of 40 years showing a consistent signal for ovarian cancer in women exposed to talcum powder products.

VII. The Role of Industry in Talcum Powder Product Safety Assessments

77. In support of my opinions, I have reviewed and considered thousands of documents related to the actions of Johnson & Johnson, Imerys, and PCPC with respect to talc and human health risks and safety assessment. The documents related to Johnson & Johnson date back into the 1950's and 1960's (*e.g.,* patents filed by the company; studies published by company employees; internal company documents). Documents related to Johnson & Johnson and the PCPC date back to the 1970's (*e.g.,* internal company documents; exhibits to depositions of company employees or corporate representatives). Documents related to Imerys and the PCPC date back to the 1990's (*e.g.,* internal company documents; exhibits to depositions of company employees or corporate representatives). The evidence shows that the defendants worked both individually and collaboratively to present a uniform position to regulators, the scientific and medical community, and consumers, that talcum powder product use did not present a risk of ovarian cancer in humans.

78. Evidence supporting Johnson & Johnson's early efforts to influence the safety information disseminated publicly about talc in the late 1970's involved the 1975 U.S. Pharmacopeia (USP) listing for talc. Based on their efforts, the USP listing was changed in 1980 to omit the warnings *"Do not apply to open wounds"* and *"Do not inhale"* (JNJ000343613;

JNJNL61_000030770; JNJ000343580; JNJ000343612; JNJ000343614; JNJ000343946; JNJ000343611; trial testimony of Dr. John Hopkins dated February 8, 2018). Johnson & Johnson relied on their assertion that there was no asbestos present in talc that met the USP standards, even though evidence shows they were aware of the presence of some level of asbestos in their products at that time (as discussed above). Moreover, by the 1970's Johnson & Johnson was aware that some scientists believed that exposure standards for asbestos should be applied to fibrous talc (JNJ000231422-428). Evidence suggests that industry knew or should have known about the significant human health risks posed by exposure to cosmetic talc body powders well before 1975. Therefore, the evidence suggest that Johnson & Johnson failed to provide accurate information to the USP regarding the issue of the presence of asbestos in talc. Moreover, in asserting that *"normal exposure to cosmetic talc presents no inhalation hazard"* (JNJNL61_000030770), the company was making statements that were not scientifically defensible given the knowledge available by 1975 concerning talc and the hazards of inhalation exposure (as discussed above). Therefore, it is my opinion that Johnson & Johnson knew or should have known that use of cosmetic talc body powders had been reported to lead to lung injury when the talc was inhaled, and to lead to adverse tissue reactions when internal tissues were exposed to talcum powder products.

79. Also, in the 1970's, documents show that Johnson & Johnson made efforts to influence the science around the issue of asbestos in talc and the link of talc with ovarian cancer (P-0055; P-0344; P-0002). The efforts included a discussion with the FDA Commissioner in 1974 where Johnson & Johnson stated: *"Our very preliminary calculation indicates that substantial asbestos can be allowed safely in a baby powder."* (P-0660). Later in the same document Johnson & Johnson states that *"if the results of any scientific studies show any questions of safety talc, Johnson & Johnson will not hesitate to take it off the market"* (P-0660). Given the fact that Johnson & Johnson was aware, or should have been aware, of the science that had accumulated by that time linking asbestos exposure with both ovarian cancer and lung cancer, the position by the company regarding the presence of any asbestos in talc body powders is inconsistent with protecting public health when the issue involved exposure to a cosmetic product, one without any benefit. Importantly, consumers were not informed of the safety concerns regarding the presence of asbestos in talcum powder products.

80. In discussing the issues related to industry and its actions to influence the public perception of talc safety, it is important to understand the role of the CIR in cosmetic ingredient safety assessments. As already mentioned above, the CIR process is industry-funded and is administered independent of the FDA. While FDA may consider CIR conclusions, the FDA does not adopt their findings (PCPC_MDL00096145, PCPC_MDL00044971, Deposition of Dr. Linda Loretz). The panel's role is to review the available safety information for the ingredient and to come to a consensus about its safety. The CIR reports are open for public comment before they are finalized. Over the years, the CIR has reviewed and reported on over 5,000[55] ingredients, yet only 12 have been found to be *"unsafe"* for use.[56] The current CIR meetings involve no more than two days of discussion for ingredients and ingredient groups (talc was one ingredient amongst a multitude of ingredients in 17 ingredient groups) during which time the panel reviews the data and comes to its conclusions regarding ingredient safety (deposition testimony of Dr. Linda Loretz October 1 and 2, 2018). None of the CIR expert panel members personally review the relevant published studies; instead, the members review only the report drafted by CIR staff (transcript of the testimony of Dr. Andersen at pages 3157-3158, *Echeverria v. Johnson & Johnson*). This is a much more abbreviated review process than is employed by IARC when it is making a cancer hazard assessment.[57] For example, in the IARC reviews, the Working Group, drafts the consensus document as a group while working together for seven to eight days (MDL_KELLY00002701-2702). Care is taken to ensure that detailed summaries of studies are written by relevant experts, unlike the CIR reports which are written by employees of the PCPC instead of the experts on the panel. Also, unlike the IARC review process, where panel members chosen for a review are ones with specific expertise in the scientific issues that are addressed for a chemical (IARC, 2006), the CIR panel typically includes less specialized scientists; and the make up of the panel changes little from meeting to meeting even though the issues raised for individual ingredients could be very different (deposition testimony of Dr. Linda Loretz in 2018). Therefore, from a scientific perspective, the IARC process involves a much more detailed scientific evaluation of the issues surrounding a cancer hazard than the issues addressed by any CIR review.

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[55] Testimony of CIR Director from 1993 to 2013, Dr. Alan Andersen dated 8/10/2017 (Echeverria v. Johnson & Johnson).
[56] https://www.cir-safety.org/cir-findings
[57] See description of the process at: http://monographs.iarc.fr/ENG/Preamble/currentbscientificintro0706.php

81. In deposition testimony over several days in 2018[58], corporate representatives of the PCPC provided detailed descriptions of the CIR process. The testimony of the former Director of the CIR (Dr. Andersen in *Echeverria v. Johnson & Johnson* dated 8/10/2018) also provided details about the CIR process, including the talc process, and the close relationship with industry. Additional information can be found in internal company documents as well (*e.g.*, P-0561; P-0595). The lack of independence of the CIR process from PCPC operations and influence by industry is apparent after review of these sources, even though a different impression is given through the CIR website. For example, at the CIR website the following is stated:

> *"The Cosmetic Ingredient Review was established in 1976 by the industry trade association (then the Cosmetic, Toiletry, and Fragrance Association, now the Personal Care Products Council), with the support of the U.S. Food and Drug Administration and the Consumer Federation of America. Although funded by the Council, CIR and the review process are independent from the Council and the cosmetics industry."*

As will be discussed below with respect to the talc CIR review, the process was not independent of industry, did not include physicians with expertise in gynecological cancer or female pelvic anatomy, and involved a truncated discussion among the panel members as compared to the IARC assessment process.

82. The CIR has set forth procedures for its safety assessments (CIR 2018; IMERYS 118788). As discussed in the CIR procedures document, the purpose of the CIR is to *"determine those cosmetic ingredients for which there is a reasonable certainty in the judgement of competent scientists that the ingredient is safe under its conditions of use"*. The same document defines "safety" or "safe" to mean that there is *"**no evidence in the available information** that demonstrates or suggests reasonable grounds to suspect a hazard to the public under the conditions of use that are now current or that might reasonably be expected in the future" [**emphasis** added]*. Based on this definition of *"safe"* and the purpose stated by the CIR, this means that the standard applied to a CIR review, and that should guide the outcome of that review, is whether there is evidence that demonstrates or suggests a hazard. If there is any such evidence

[58] Dr. Linda Loretz of the PCPC was deposed as a corporate representative of the PCPC on 17 July 2018, 1 October 2018, and 2 October 2018. Mr. Mark Pollack was deposed as a corporate representative of the PCPC on 28 July 2018.

of a hazard under conditions of use, then the standard would not be met, and the ingredient should not be deemed safe for use in cosmetics.

83. In the case of talc, a final version of the CIR panel report was published in 2013 (CIR, 2013) and then appeared in the published literature in 2015 (Fiume *et al.* 2015). The CIR panel stated that talc is *"safe in the present practices of use and concentration in cosmetic products"* (CIR, 2013). There was no CIR report published on talc before 2013 even though there was evidence for concern about the safety of talcum powder products that had been voiced within the scientific community for decades and that reliable evidence had been published in peer-reviewed journals even before the CIR came into being in 1978 (as discussed above). Based solely on the CIR standard for safety, existing evidence provided a reasonable basis for finding that the perineal use of talcum powder products increases the risk of ovarian cancer. Moreover, as discussed above with respect to the issue of talc migration, I described how that assessment was incomplete and resulted in conclusions that are not supported by available science.

84. Important evidence in support of my opinions comes from admissions contained in documents and testimony by the trade organization known in the past as the CTFA, and since 2007 known as the PCPC. Publicly available documents show that PCPC has been intimately involved with talc safety issues over the period from the early 1970's up to today (see deposition testimony of Dr. Linda Loretz, page 700). Together with Johnson & Johnson and Imerys, PCPC coordinated and presented a position to regulators and the medical community that talc was safe. This position was presented regardless of significant evidence to the contrary.

85. In their deposition testimony in 2016 and 2018, Mr. Mark Pollak and Dr. Linda Loretz, the designated PCPC corporate representatives, provided details on the close relationship between the CIR panel work generally and the PCPC, as well as the talc review itself. Other documents available for review confirm the close relationship (*e.g.,* IMERYS 329339 through 329342; IMERYS315001; IMERYS320614; IMERYS281069; IMERYS281536; IMERYS283501; IMERYS322846; IMERYS298968; IMERYS065205; IMERYS118788; PCPC_MDL00103539; PCPC_MDL00009859; PCPC_MDL00009893; PCPC_MDL00009914; PCPC_MDL00009950). This is an important consideration in this case given the role that the CIR

plays in cosmetic safety assessments, assessments that are used by manufacturers to assert that their ingredients are safe as required by FDA.

86. Testimony and admissions from PCPC corporate representatives including exhibits to their depositions, are relevant to my opinions because they outline the level of influence on the purportedly independent processes for talc safety assessment by the CIR. To start, the PCPC's president is the chairman of the CIR steering committee that is responsible for choosing the experts that are on the CIR panel, including the talc review in 2013 (deposition of Dr. Loretz pages 842-845; IMERYS118788; trial testimony of Dr. Andersen dated 8/10/2018 at pages 3130-3031). The CIR review documents are written not by the expert panel but by CIR staff, who are employees of the PCPC (PCPC0004567; IMERYS118788; trial testimony of Dr. Andersen 8/10/2018). The CIR panel scientists are a standing committee, meaning that the scientists involved do not change that much from review to review, regardless of the issues to be addressed (deposition of Dr. Linda Loretz pages 842-845; trial testimony of Dr. Andersen 8/10/2018 pages 3132-3133). This is important because the issues related to talc safety are not the typical issues linked to cosmetic ingredients. For most cosmetic ingredients, the issue is not migration internally after perineal application or even use of large amounts of product that can easily suspend in air with each use. Additionally, much of the data that was important in the evaluation of talc as an ingredient in body powders and perineal dusting was human epidemiological data. Yet, the expert panel reviewing talcum powder products and talc as an ingredient in those powders did not include anyone with specific expertise in the unique exposure issues presented or expertise in epidemiology (deposition testimony of Dr. Loretz pages 781, and 838-842). All CIR panel members are paid through the PCPC which in turn is funded by industry, including Johnson & Johnson and Imerys[59]. In fact, records show that many of the CIR panel members made tens of thousands of dollars each year that they served on the CIR panels (deposition testimony of Dr. Loretz pages 964-974), and that Johnson & Johnson and Imerys were major sources of funding for the PCPC (deposition testimony of Dr. Loretz pages 829-834) and, consequently, the CIR panel activities. The CIR review of talc

[59] Although Imerys is no longer a member of the PCPC (see deposition testimony of Dr. Loretz), Imerys was a member of the PCPC during the years that talc safety was at issue (1980's, 1990's, 2000's) and during the time of the CIR review of talc (2010-2013). See also IMERYS311275.

was initially started in 2009 but was put on hold for three years before beginning again in 2012 (trial testimony of Dr. Andersen dated 8/10/2018 page 3148).

87 Another example of influence on the FDA comes from the industry's response to the filing of two Citizen's Petitions related to adding a cancer warning to talcum powder products. Before continued discussion of the CIR process and industry influences, these events should be examined. This was discussed in the deposition of Dr. Linda Loretz on October 1, 2018.

88. Two Citizen Petitions were filed related to cosmetic talc products, one in 1994 and a second in 2008. In 2014, the FDA finally issued a response to those Petitions. In my experience, this is a very long time to wait for an FDA response. As background, the Citizen's Petition process is one that anyone outside of the FDA can use to ask FDA to take, or refrain from taking, an action related to any of the products regulated by FDA (21 CFR Part 10). The two Citizen Petitions were filed by the *Cancer Prevention Coalition,* and both related to adding a cancer warning to cosmetic talc products. In the case of the 1994 Petition, Dr. John Bailey, then Acting Director of the Office of Cosmetics and Colors within CFSAN at FDA, responded to the November 1994 Petition on July 11, 1995. Dr. Bailey stated that FDA had not been able to reach a decision on the Petition within the first 180 days of the filing (as required by the regulations) and the reason given was *"because of the limited availability of resources and other agency priorities"* (P-240). In the case of the 1994 and the 2008 Petitions, the FDA did not formally respond to the Petitioner until April 1, 2014 (P-47). The FDA's 2014 response indicated that FDA was not requiring addition of the specific cancer warning requested by petitioner.

89. In support of my opinions regarding the influence of industry on FDA's actions are the following accounts. In July 1994, six months after the filing of the first Citizen's Petition, a meeting sponsored by both FDA and industry (including Defendants in this case) was held that focused on the safety of cosmetic talc. A delegation from PCPC (staff of the PCPC, members of the organization, as well as consultants) met with representatives of the FDA (John Bailey[60] and

[60] This is the same John Bailey that a few years later leaves FDA and becomes a senior staff member of the PCPC.

Ron Lorentzen) and representatives of the NTP (Dr. Gary Boorman[61]) to discuss the NTP talc study data (JNJ000016687 through 688). Contained in the minutes to that meeting, PCPC reported that FDA admitted they were under pressure from within the agency to fully investigate the association between talc and ovarian cancer. Topics of discussion at the meeting were directed towards the use of the NTP study tissues for further analysis to help "reduce uncertainty about human risk", whether it was feasible to analyze rodent tissues for the presence of talc particles, whether if analytical procedures for rodent tissue analysis were set up by FDA/ NTP it would be feasible to analyze human ovarian tissue, and what issues or problems might be raised by such studies. Interestingly, the PCPC stated in the meeting minutes that the discussion around analysis of talc in the animal tissues *"seemed to dampen enthusiasm by Dr. Novotny for conducting analysis of human tissue"* (JMJ000016688). The only work product resulting from this meeting appears to be the NTP's analysis of archived ovarian tissue samples from rats and mice that were part of the NTP study (Boorman *et al.* 1995; the paper was submitted in October 1994 to the journal *Regulatory Toxicology and Pharmacology* and the concerns with this journal regarding talc safety is discussed below in paragraph 91). No work on human ovarian tissue analysis appears to have been initiated at this time.

90. The influence of industry on FDA actions was evident in the early 2000's during the time when the NTP was considering the addition of talc to the Report on Carcinogens. In an e-mail dated 17 October 2000 (JNJ000013664 through 665), the PCPC was discussing the NTP's recent draft background document on talc wherein the NTP scientists concluded that *"non-asbestiform talc is reasonably anticipated to be a human carcinogen"* and proposed listing the ingredient in the 10th Report on Carcinogens (RoC). This e-mail was directed to gathering funding commitments from industry to undertake actions aimed at stopping the listing proposed by NTP. This e-mail was followed by further communications on same topic later in October of 2000 (IMERYS303895 through 898) where industry representatives discussed experts that could assist in their efforts but where they also acknowledged that a new study had been published concerning the mortality of German rubber workers that had been exposed to talc and asbestos dust (combined dust exposure) where the results were stated to be *"not very good for the talc industry."* The issue

[61] Other NTP staff were there as well, as were a pathologist from the University of North Carolina (there to discuss analysis of human tissues in a future study) and an epidemiologist from NIEHS.

was stomach cancer mortality was important because, as the employee of Luzenac Europe[62] explained, an internal study that the company had failed to publish also found an association between talc dust and stomach cancer; this information would not have been available to the FDA or the NTP. In an e-mail dated February 5, 2001, PCPC again was discussing the NTP process and the need to "pressure" the NTP to include Dr. John Bailey in its Executive Committee meeting, where it would be decided whether to accept the recommendations for a listing of talc in the 10th RoC. Note that, as discussed in more detail in paragraphs 94-96, NTP deferred the listing of talc as part of the 10th RoC.

91. Industry influence on FDA actions also was evident in 2008. On May 8, 2008, the PCPC attended a meeting with FDA to discuss the FDA response to the 2008 Citizen's Petition (PCPC0061912 through 916[63]). The meeting minutes state the meeting's purpose: *"The Council requested the meeting solely to present scientific data to support the safety of talc and at the request of the Talc Interested Party."* (PCPC0061912). A review of the minutes to the meeting show that the PCPC and other industry representatives failed to provide FDA with accurate description of their knowledge of cosmetic talc safety; examples would be their knowledge that US samples of cosmetic talc were not asbestos-free (some asbestos had been detected), and the issues behind NTP's failure to list talc in its *10th Report on Carcinogens*. An email dated November 3, 2008, reveals Kathy Wille, Senior Director, Scientific and External Regulatory Policy, Product Stewardship, from Johnson & Johnson, had another interaction with FDA later in 2008. The e-mail states: *"had a side conversation with a key figure from the FDA cosmetic group that is responsible for responding to the Citizen's Petition."* The email further states: *"He indicated that the FDA would rule against the petition and would not require warning labels on cosmetic products. But the FDA is looking for* ***scientific support*** *from industry that will help justify their position. She suggested that there is a collective group working to have comments submitted to the FDA."* (IMERYS 250983; IMERYS 281179). *[**emphasis** added]* In her 2021 deposition testimony, and affidavit executed in 2018 (affidavit of August 24, 2018; DX-1097), 10 years after this reported encounter, Kathy Willie denied that she had such a side conversation with FDA. On

[62] This company was a sister company to Luzenac in the US which was a predecessor to Imerys.
[63] At the meeting were PCPC employees including Dr. John Bailey, formerly head of the FDA's Office of Cosmetics and Color, and Dr. Linda Loretz, Dr. Kathy Wille, an employee of Johnson & Johnson, Dave Mallon an employee of Unilever, and Craig Bernard a Shirpal Shirma, and two employees of Rio Tinto (Imerys) that joined by phone.

July 21, 2009, the PCPC submitted comments on the Petitions to FDA (PCPC_MDL00015494; P-342). A review of the cover letter for the comments reveals that Dr. John Bailey, the same Dr. Bailey that was Acting Director of the Office of Cosmetics and Colors in 1995 and that responded to the first Petition by the Cancer Prevention Coalition, signed the 2009 letter as an employee of the PCPC. The letter was accompanied by a report prepared by Dr. Michael Huncharek and Dr. Joshua Muscat, consultants that had been hired by the PCPC to prepare a response. The defendant's response to the Citizens Petition contained misleading and inaccurate information, including that asbestos had been eliminated from talc which was an issue that was of concern to the FDA (see deposition of Dr. Linda Loretz).

92. Other documents reveal that Dr. Huncharek and Dr. Muscat had been working as consultants for Johnson & Johnson and Imerys for years (*e.g.,* JNJ000377405; JNJ000375565; JNJ000391641; deposition of Dr. Muscat dated September 25, 2018), providing the companies and/or the PCPC with consulting services related to talc and cancer risk as part of the NTP process in 2000 and 2005 and the IARC process in 2006 (see deposition testimony of Dr. Nicholson dated July 26, 2018; deposition testimony of Dr. Linda Loretz, Ph.D. October 1, 2018; deposition testimony of Dr. Muscat dated September 25, 2018, among others), as well as the talc Citizen Petition response process. Another document shows that in May 2009, PCPC members, including Johnson & Johnson and Imerys, met with FDA to discuss their comments before they were submitted in July 2009 (PCPC0028174-28176; JNJ000092018), even though FDA denied the *Cancer Prevention Coalition* the opportunity for a public hearing to discuss their scientific evidence that the Petitioner had requested both in 1994 and in 2008. The failure of FDA to afford the Petitioner a public hearing and request a more detailed examination of the Petitioner's scientific evidence to elicit a response to questions raised about talc safety in 1994 and in 2008 resulted in a process wherein industry was the sole source of information.

93. The evidence reviewed shows that the FDA did not hold a public hearing which would have allowed for more detailed input from scientists outside of industry. Moreover, as discussed above in some detail, the FDA was not, and has not even today, provided with all available evidence of the existence of the presence of toxic constituents such as asbestos in cosmetic talcum powder products. As a result, it is my opinion that the conclusions reached by

FDA in its 2014 response were not based on an accurate and complete understanding of the composition of talcum powder products. In addition, evidence shows that the FDA was not fully informed about the key role that certain industry consultants had played in generating some of the scientific studies and review papers that industry has used to support their assertions regarding the safety of talc. For example, the 2003 paper by Huncharek and colleagues (Huncharek *et al.* 2003. *Anticancer Res*. 23:1955-1960) failed to acknowledge that industry had provided support for their work, while later papers failed to acknowledge the full list of industry sponsors of their work (*i.e.,* Huncharek *et al.* 2007. *Eur. J. Cancer Prevent*. 16:422-429; Muscat and Huncharek. 2008. *Eur. J. Cancer Prevent*. 17:139-146; Huncharek and Muscat. 2011. *Eur. J. Cancer Prevent*. 20:501-507; see deposition testimony of Dr. Nicholson dated July 26, 2018). A 2005 response written by Dr. Muscat and Dr. Huncharek to critique the work of Dr. Cramer (Muscat and Huncharek, 2005) also failed to disclose the financial relationship between his work and industry (JNJ000368327; see depositions of Dr. Nicholson and Dr. Loretz). Related activities included the work of Huncharek and Muscat with respect to critiques of Dr. Cramer's work on the talc and ovarian cancer issue. An e-mail dated 30 September 2008 from Dr. Muscat to employees of Johnson & Johnson (JNJ000368327) reveals that Dr. Muscat clearly understood the importance of Dr. Cramer's positive study results concerning the association between genital talc use and ovarian cancer. The e-mail also addressed the data from the Nurse's Health Study (abbreviated as "NHS" in the e-mails), a cohort study which was described as a major reason why IARC in 2006 failed to assign a rating higher than "2B" to talc. Despite the evidence of an association seen in the Cramer study Dr. Muscat chose to ignore the Cramer results and presented a one-sided presentation of the scientific evidence to the FDA.

94. Prior to the CIR review of talc, there were significant events in the 1980's and early 1990's that triggered the need for a safety assessment of the products. The NTP had performed cancer studies in mice and rats in the 1980's that were published in 1993 (NTP, 1993; the report was discussed in detail above). In addition, by 1993, several scientific and/or epidemiological studies had appeared in the scientific literature linking perineal talcum powder product use with ovarian cancer in women (*e.g.,* Henderson *et al.* 1971; Cramer *et al.* 1982; Hartge *et al.* 1983; Whittemore *et al.* 1988; Booth *et al.* 1989; Harlow and Weiss, 1989; Harlow *et al.* 1992; Chen *et al.* 1992; Rosenblatt *et al.* 1992). As a result, a workshop was held in 1994 that was sponsored by

industry and the FDA (PCPC_MDL00026142; PCPC_MDL00028481; PCPC_MDL00028665; PCPC0072694; PCPC0075364; P-14). FDA's opening remarks at the workshop indicated that the FDA was wanting input on the *"validity and significance of the existing knowledge regarding the safety of cosmetic talc"* (Carr, 1995). The workshop was run by a group known as the ISRTP, the *International Society for Regulatory Toxicology and Pharmacology*. The ISRTP has been described as *"an association dominated by scientists who work for industry trade groups and consulting firms"* (Michaels, 2008; Michaels, 2020). Sponsors of the organization in the past have included major tobacco companies, chemical companies, and drug manufacturing companies (Axelson *et al.* 2003). The ISRTP also publishes a journal (*Regulatory Pharmacology and Toxicology*) and as pointed out by Axelson and colleagues (2003) the articles published often failed to list complete conflicts of interest disclosures. As a result, the ISTRP's activities have been questioned in terms of the level of industry influence that exists (Axelson *et al.* 2003).

95. The ISRTP talc workshop was held in 1994 (January 31 to February 1). The minutes to the meeting are available for review as are the papers that were published after that meeting in the ISRTP journal (1995; volume 21; pages 211-260). One day of the meeting was devoted to the issues related to the NTP cancer studies with talc and the issue of mechanisms of lung carcinogenesis (January 31, 1994), while the second day was devoted to the epidemiological data that had accumulated with respect to talc exposure in women and ovarian cancer and the issue of talc migration (February 1, 1994). Industry-sponsored scientists were among those attending and making comments during the meeting (P-0017). My review of the minutes to the workshop (PCPC0076689-76908; JNJ000008704-8864) as compared to the published summary of the workshop (Carr, 1995) reveals important differences in the actual statements made by scientists at the meeting and the published paper. The paper acknowledges that not all presentations were published. The workshop attendees are listed by Dr. Carr (Carr, 1995) and included 109 participants. At least 67 were from industry or were consultants to industry. Other participants were from government agencies (25 participants) and from academics or public interest groups (17 participants). Key differences in the minutes versus the published summary of the meeting included the fact that not all participants were present at the end of the meeting when the group discussed the workshop findings. Contrary to the statements in the Carr publication regarding *"unanimous assessment"* (Carr, 1995), the statement made on the second afternoon of the

workshop was as follows: *"It is not our intent, certainly not mine to strive for consensus, either as a unanimous consensus or a partial consensus which I understand you have to have to use now in describing a consensus…"* (JNJ000008843). Questions were raised by scientists at the meeting on the first day related to the fact that the animal data had limitations but that it still had relevance in terms of raising questions about the ability of talc to cause lung injury that could lead to cancer. On the second day, one speaker, Dr. Austin, indicated the epidemiological data provided some evidence of an association between talc and ovarian cancer (JNJ000008727). Then, Dr. Brown, another presenter, discussed the issue of talc migration to the ovaries and specifically stated *"the summary of my conclusions is that I believe it can"* (JNJ000008734)). In contrast, the Carr publication states: *"Following a presentation by Dr. Brown (University of Wisconsin), the discussion made it clear that available histologic and physiologic studies provide no basis to conclude that talc can migrate to the ovaries from the perineal region"* (page 215 of Carr, 1995). Thus, based on the large amount of information that was not discussed at the ISRTP workshop but was known to industry, it is my opinion that the Carr publication fails to provide an accurate and complete description of the state of the science with respect to talc safety in 1994. Moreover, an important outcome of this workshop was that the signal of talc and human cancer risk existed and could not be ruled out based on discussion at the workshop.

96. Additional evidence which supports my opinions comes from documents describing the industry response to the 1993 NTP publication of findings on talc and cancer in rodents, wherein the NTP concluded that talc was carcinogenic in animals. PCPC along with industry members re-activated the group known as the Talc Interested Party Task Force (*e.g.,* P-14; P-83; P-57; JNJ000016687 through 688). The Talc Interested Party Task Force was first established in the 1970's and reconvened in response to the publication of the paper by Dr. Cramer (Cramer *et al.* 1982), where use of cosmetic talc had been linked with ovarian cancer (P-0845). At this time, the group was led by Johnson & Johnson and the talc ingredient supplier Imerys. Documents from that time show that the goal was to mount a defense strategy around talc and to ensure that the products continued to be sold without regulation (*e.g.,* P-57; P-122; P-86; P-87; P-88; P-90; P-20; JNJ000016687 through 688). Yet, at least in the case of Johnson & Johnson, an outside consultant that had worked with the company for years on talc issues (Dr. Wehner) had suggested in 1994 that studies be performed to answer questions about talc safety, specifically with

respect to the risk of ovarian cancer (P-0435). From my review of the depositions and documents, there is evidence that industry had no interest in sponsoring any new research or did not want to spend the money on such research (P-32, deposition of Dr. Linda Loretz). As previously mentioned in paragraph 21 (above) it is the manufacturer's duty to conduct whatever testing is necessary to ensure the safety of their products. Evidence in this case shows that Defendants failed to perform such testing, despite awareness of safety concerns with cosmetic talc.

97. In formulating my opinions, it was relevant to consider evidence surrounding the activities by industry in the 2000's when NTP was considering whether or not to classify and list talc as a carcinogen as part of its Report on Carcinogens process. As of 1978, Section 301(b)(4) of the Public Health Service Act, as amended, requires that the Secretary of the Department of Health and Human Services (DHHS) publish an annual report on substance use and abuse. The Report on Carcinogens (RoC) is a report that lists all substances that are known to be human carcinogens or may reasonably be anticipated to be human carcinogens. As discussed on the NTP website[64], the first RoC was published in 1980, and since that time, the process has evolved in terms of the way that reviews are performed. In the early RoC process (up through the 7th RoC in 1994), there were formal listing criteria and two categories *("known human carcinogen"* and *"reasonably anticipated to be a human carcinogen"*) that were determined based on evaluation of cancer studies in humans and/or experimental animals. Starting with the 8th RoC process, the criteria for listing were expanded to include consideration of all relevant information such as mechanistic data. During the period that talc was reviewed as part of the 10th RoC in 2000, the review process included two federal review groups providing initial input on listing recommendations, followed by review by the NTP Board of Scientific Counselors Subcommittee that provided input on listings in a public forum, giving additional opportunities for public and/or industry input. As a result, the first two reviews undertaken were by government scientists and free from outside influence, while the last step in 2000 involved public input and review by a Board that included members from industry (as discussed in more detail below).

98. Deposition testimony and documents show that, in the context of my opinions that industry undertook significant efforts to influence regulatory bodies and the science concerning

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[64] https://ntp.niehs.nih.gov/pubhealth/roc/history/index.html

the safety assessment of talcum powder products, the Center for Regulatory Effectiveness (CRE) played an important role. Based out of Washington, DC, the CRE is a "consulting firm" (http://www.thecre.com/about.html; C&M-LUZ 00013326; IMERYS 226115). The CRE's primary purpose is to provide advice to companies and to intervene on regulatory issues that threaten their business (IMERYS 226115). With respect to talcum powder products, documents show there were two individuals from CRE that were involved: the company's founder and owner, James "Jim" Tozzi and William "Bill" G. Kelly, Jr. Imerys initially retained the CRE in 2000 to assist with the 10th RoC process at NTP (IMERYS 100237) and the CRE's consulting work with Imerys continued for more than a decade. Yet, documents show that the CRE represented themselves as being an *"independent"* organization and *"not affiliated"* with any particular industry, company, or other entity. (IMERYS 100151 and MDL_KELLY00014222). Documents also show that CRE efforts on behalf of Imerys led to sufficient confusion regarding the definition of talc such that NTP's Executive Committee reversed the scientists' classification of talc as a carcinogen (IMERYS 330351, IMERYS 303828, IMERYS 110806, IMERYS 209930). CRE efforts on behalf of industry continued with their interaction with the CIR and the production of the 2013 CIR safety assessment of talc (IMERYS 226115; MBS-CRE000031, MDL_KELLY00017550, MDL_KELLY00014222, MBS-CRE000271).

99. There had been 15 RoC processes up to 2021, the 15th RoC being published in December 2021. No additional RoC reports were publicly listed at the NTP website as of May 2024. Talc was considered as part of the 10th and 12th RoC processes. The 10th RoC meeting where talc was discussed was held in 2000, while the 12th RoC meeting was held in 2005. The 10th RoC deferred action to list talc as a carcinogen, citing a need for additional information; the 12th RoC also deferred action to list talc. It is important to note that the NTP RoC nominated talc for consideration for listing in the 10th RoC based on a review of the available data by a body of scientists without input from industry, and without any direct interaction with other industry groups or representatives with a conflict of interest, consistent with the procedures set forth by IARC for its cancer reviews (IARC, 2006). It is also important to note that a review of the minutes of the 10th RoC indicates that even though the only public comments made to the panel were from industry representatives, many of the reviewers supported listing non-asbestiform talc as reasonably anticipated to be a human carcinogen (IMERYS 039060 through 085). During the 2000

NTP review of talc for listing in the 10th RoC, it is my opinion that Imerys, the PCPC, and Johnson & Johnson made efforts to influence the process and prevent talc from being listed as a carcinogen (*e.g.,* P-0255; P-0012; P-0013; P-0089; P-0317). Documents show that Imerys, with the full knowledge of Johnson & Johnson and PCPC, hired the Center for Regulatory Effectiveness (CRE) in 2000 to submit comments to influence the RoC process without disclosing that defendants coordinated and were directly involved in both the strategy for and the drafting of those comments (IMERYS024243; IMERYS-A_0024244; JNJ 000242897; JNJ 000404803; JNJ 000001699; PCPC0072893; NTP Summary Minutes, Dec. 13-15, 2000). This effort to influence the process continued into 2001 when the Executive Committee of NTP met and made the decision to defer talc even though the scientists that had reviewed talc had overwhelmingly voted to list talc as a carcinogen (*e.g.,* IMERYS024367; IMERYS 303895-898; P-27; JNJ000013664; JNJ000404511-512; PCPC0066630-672; IMERYS-A_0024411; IMERYS303842; IMERYS288570; IMERYS239852; IMERYS239750; IMERYS239749; IMERYS026529; IMERYS024243; JNJ000008350; JNJ000008344; JNJ000000636; JNJ000368187; JNJ000404425; NTP minutes 2000; IMERYS303828; IMERYS179104; IMERYS208830; IMERYS-A_0024244; PCPC0035777; PCPC0066630). At least by 2002, evidence shows that Imerys was aware of the consequences of listing talc as a carcinogen in terms of product liability issues (P-26; P-3). Evidence shows that industry was aware that, the NTP was more vulnerable to such influence than other bodies such as IARC (P-27). Additional documents provide evidence that efforts to influence the NTP cancer listing process by industry continued in 2004-2005 when talc was scheduled to be considered as part of the 12th RoC process (JNJ00003646-348; IMERYS288692; IMERYS271234; IMERYS035406; JNJ000003436; JNJ000003472; JNJ000375565; JNJ000369203; IMERYS287089; IMERYS324762; IMERYS 236653).

100. IARC has reviewed talc twice, and its conclusions were published first in 1987 and again in 2010.[65] In contrast to the CIR review process which involved a much more cursory review of the science behind over 5000 cosmetic ingredients in the 40 plus years of its existence and only 12 were found to be unsafe for use in cosmetics, IARC was founded in 1965 and in that time has published 122 volumes describing the cancer hazard posed by 1016 different compounds. Of those

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[65] IARC's website indicates that IARC will be evaluating talc and carcinogenicity again in June of 2024 (https://monographs.iarc.who.int/news-events/meeting-136-talc-and-acrylonitrile-is-announced/).

compounds reviewed by IARC, 120 were found to be *"carcinogenic to humans"*, 82 were found to be *"probably carcinogenic to humans"*, 302 were found to be *"possibly carcinogenic to humans",* 501 were found to be *"not classifiable as to its carcinogenicity to humans",* and one compound was found to be *"probably not carcinogenic to humans"*[66]. IARC focuses solely on the issue of cancer hazard and prioritizes its reviews based on compounds where evidence has accumulated indicating there may be a cancer hazard.

101. In the first assessment of talc (IARC, 1987), the panel met in 1986 and concluded that there was sufficient evidence for human carcinogenicity for talc containing asbestiform fibers (asbestos and fibrous talc) but inadequate evidence for talc not containing asbestiform fibers. Talc with asbestiform fibers was listed as Group 1 (known human carcinogen); talc without asbestiform fibers was listed as Group 3 (not classifiable as to human carcinogenicity). The IARC classification system used to define evidence of carcinogenicity was discussed by Johnson & Johnson in a 2002 communication from Bill Ashton, an employee of Johnson & Johnson:

> *"IARC classified crystalline silica as a potential human carcinogen in 1986. That same year they reviewed talc and concluded there was "inadequate evidence" to classify talc as a potential human carcinogen.* ***That was not a "non-carcinogen classification"****; it just means they did not have enough evidence to conclude that talc was a potential carcinogen. In 1986, they also concluded that "talc containing asbestiform fibres" was a known human carcinogen." [****emphasis**** added]*

In 2006, IARC again considered the classification of talc as a carcinogen. The working group considered a large body of data available up until 2006, which included a large group of human epidemiological studies examining the risk of ovarian cancer with perineal talc use in women. Although industry was aware that the IARC process was less political (P-27), evidence shows that, consistent with my opinions regarding industry's influence on the talc regulatory processes, industry still initiated efforts to influence the science surrounding talc and cancer risk (JNJ000003914-315; JNJ000004015-4019; JNJ000003969; JNJ000369087; JNJ 000003911; JNJ 000003969). These efforts included having Dr. Muscat, a consultant to industry (IMA-NA0000571; JNJ000369543; deposition of Joseph Muscat; Muscat000001494; Muscat000001204) attend as an observer and to attempt to influence reviewers with his comments.

[66] https://monographs.iarc.fr/agents-classified-by-the-iarc/

Other documents provide additional information about the attempts by industry to influence the IARC process in 2006 (*e.g.,* P-0650; P-0204; P-0035; WG-IMA-NA0001554). It is notable that the IARC panel, with less chance of outside influence being asserted, listed talc without asbestiform fibers as a carcinogen (Group 2B; possibly carcinogenic to humans). Following the IARC classification of talc, Imerys elected to add a cancer listing to its MSDS sheet for talc as a possible human carcinogen. Johnson & Johnson has refused to do the same on its MSDS for finished products (JNJ000390337-338; JNJ4T5_000004521-522). The failure of Johnson & Johnson to warn consumers, and even workers that are involved in handling of their products, about the cancer risk associated with use or exposure to talcum powder products is a public health concern. In addition, when talc was listed as a possible human carcinogen by IARC in 2006, documents show that industry continued to promote a message about talc safety by recruiting scientists to publish articles that raised doubt about the link of perineal talc use and ovarian cancer (*e.g.,* P-78; P-92).

102. Returning now to consideration of the CIR process for talc in 2012-2013, documents suggest that industry was intimately involved with the CIR process and its review of talc safety. Important details related to the influence exerted by industry on the overall CIR process as well as the talc review itself is found in the trial testimony of Dr. Alan Andersen (dated August 11, 2017). Dr. Andersen was in charge of the CIR process and was an employee of the PCPC. Dr. Andersen was responsible for implementation of the talc CIR review process. His testimony and the accompanying documents showed that at least two of the CIR expert panelists that he allowed to participate had conflicts of interest that were not publicly disclosed, and that Mr. Kelly of the CRE provided assistance to the CIR during its talc review. Some of the language in the final CIR talc review documents was copied directly from comments made by the CRE. Additionally, Dr. Andersen was not aware of the fact that the CRE had been hired by Imerys and the talc industry to provide comments to CIR. Additionally, evidence shows that in submitting comments to the CIR, Mr. Kelly of the CRE claimed that *"The Center for Regulatory Effectiveness is not representing a particular company or industry segment in filing these comments [,]"* even though he was working for Imerys at the time (IMERYS 062429). Then, before the review even began, he commented that CRE had established a *"strong relationship with the Cosmetic Ingredient Review."* (IMERYS 226115). Monice Fiume of the CIR staff told Mr. Kelly in 2011, before the review began, *"that*

CIR would welcome any input from industry on the review at any time." (IMERYS 065205). Further evidence shows that CIR staff and not the expert panel itself, wrote the talc safety assessment report, and then provided the expert panel with that review as well as comments on the document that had only been made by industry or by consultants to industry (PCPC0004567; IMERYS14817; IMERYS118788; IMERYS065205; IMERYS315001; IMERYS320614; IMERYS281536; IMERYS283501; IMERYS322846; IMERYS298968).

103. It is my opinion as well that information contained in other industry documents, reveal industry efforts to influence scientists and regulators making decisions about talc and its human health risks, were not limited to interactions with the NTP, the FDA and the IARC panel (JNJ000024397; JNJ000379382-384; IMERYS-A_0005090; JNJ000003405; JNJ000381275-276; P-0021; P-0030; P-0031).

VIII. Talc's Human Health Risks and Regulatory Concerns

104. A review of scientific literature and internal company documents from Imerys, Johnson & Johnson, and PCPC shows that the defendants were aware of the human health hazards associated with talc powder products for many decades. Given the presence of asbestos, fibrous talc, nickel, chromium, and cobalt in the talc body powders manufactured by Imerys and Johnson & Johnson, it is my opinion that a significant human health risk was identified as a hazard related to talcum powder products use at least by the 1940's. These risks included a risk of cancer with exposure to constituents of talcum powder products, and even death with acute inhalation of large amounts of the powder. The following chronology supports my opinion that there is adequate evidence that talcum powder product use poses a hazard to human health.

- By 1940, the scientific literature contained studies showing that mineral dust exposure, including exposure to talc and asbestos, was associated with lung diseases that could be fatal, and that talc used to manufacture body powders contained both platy talc and fibrous components, including tremolite. Studies by Johnson & Johnson scientists themselves in the 1940's had identified talc as a hazard to human health (Eberl *et al.* 1948).
- By 1950, the scientific literature contained studies showing that talc was associated with adverse tissue reactions in both humans and animals, that the fibrous component of talc was of concern, that exposure to talc in the cosmetic industry itself could produce lung

disease, that lung disease due to talc and asbestos was similar, that tremolite dust was an industrial hazard in terms of lung disease, and that even small doses of talc from surgical gloves was linked with adverse tissue reactions, even being described as *"a serious menace in surgery"* (Saxen and Tuovinen, 1947) and as posing a "grave danger" (Eberl *et al.* 1948).

- By 1952, Johnson & Johnson was aware of the adverse tissue reactions linked to talc powders, including the dangers of inhalation of talc (U.S. Patent 2,626,257), even filing a patent for a replacement for talc as a medical dusting powder.
- By 1954, the scientific literature included an adverse report of death in a 10-month old infant due to asphyxiation after aspiration of a large amount of baby powder. It should be noted that reports of such deaths and serious injuries in children continued to occur into the 1960's and 1970's. In 1966, the medical community was concerned about the risks of asphyxiation and urged that talcum powder be withdrawn: *"In conclusion, it is strongly urged that talcum powder be removed from the environment of children and the traditional association of talcum powder and babies be abandoned. It has no medicinal value; wherever placed it serves as a foreign body; and at least three deaths and an unknown morbidity have resulted from this silicate powder."* Later in 1969, another physician recommended the following: *"The widespread ignorance of the dangers of talc aspiration is not surprising, and it is my opinion that these dangers should be better publicized. The direct means of accomplishing this would be a warning statement on each container."* (Moss, 1969).
- By the mid 1950's, the majority of scientists believed that asbestos could cause lung cancer, and likely other forms of cancer, in humans (Doll, 1955). Evidence for a link of asbestos exposure with lung disease, including lung cancer, was available by the 1930's.
- By the 1950's the scientific literature indicated that asbestos was present in talc, including milled powders (*e.g.,* Dreessen and Dalla Valle, 1935; Millman, N. 1947; Hogue and Mallette, 1949; Schepers and Durkan, 1955). Evidence shows that even today, talcum powder products, including products manufactured and sold by Imerys and Johnson & Johnson included asbestos, fibrous talc, nickel, chromium and cobalt.
- In 1960, the scientific literature included a paper describing the link of ovarian cancer with asbestos exposure (Keal, 1960). Given that it was known that asbestos was present in talc powder, this paper provided notice that the talcum powder products sold by Johnson &

Johnson posed a risk for ovarian cancer as well as lung cancer. Further support for the association of ovarian cancer with exposure to asbestos also was provided in the 1960's (Graham and Graham, 1967).

105. Based on the knowledge available by the 1950's, it is my opinion that talcum powder products manufactured and sold by Imerys and Johnson & Johnson should have warned consumers about the toxic constituents, such as asbestos, fibrous talc, cobalt, nickel, and chromium, in their products and the effects that could be produced by exposure to talc dusts. It is noted that in the 1953 Johnson & Johnson patent, U.S. Patent No. 2,626,257 (filed May 21, 1952), statements warning of adverse human health effects are provided including the following statement: *"Even persons who were not subjected to internal application of talcum have suffered severely from it. Talcum in the respiratory tract is dangerous and has caused severe breathing difficulties to infants, hospital patients and nurses when used carelessly and/or permitted to contaminate the air in large amounts."* Although these statements were made in the patent documents, which may have been seen by lawyers and others involved in intellectual property evaluations, no warnings related to any adverse effect of talcum powder products was made available to the scientific and medical community, regulators, and consumers through statements on packaging of Johnson & Johnson talcum powder products until the 1980's (JNJ000450199-205). Even in 2021, despite the large body of data that has accumulated since the 1950's linking talcum body powder exposure with a risk of cancer, Johnson & Johnson talcum powder products failed to warn consumers about the risks of cancer linked to talc exposure.[67] It should be noted as well that with respect solely to the presence of toxic constituents in talc such as asbestos, fibrous talc, nickel, chromium, and cobalt, and as discussed above in paragraph 19, Johnson & Johnson's failure to list those talc constituents on its labeling would be consistent with the FDA's definition of a misbranded product as well as an adulterated product.

[67] Although Johnson & Johnson recently has indicated that their talc-based body powders will no longer be sold globally (see the Press Release by Johnson & Johnson dated August 11, 2022), the talc-based powder products already released to the market and sold were not recalled by the company, As a result, any bottles of Johnson & Johnson's Baby Powder or Shower-to-Shower that remained in the market or were in the homes of consumers in 2023 would not include a warning for consumers about the risk of cancer that has been associated with use of their product.

106. The issue of safety concerns related to talcum powder products and the failure of companies to warn consumers about serious adverse health effects is of particular importance in the case of a cosmetic product, such as Johnson's Baby Powder, Shower-To-Shower and Shimmer. This is due to the regulatory process in place in the United States related to cosmetics. Unlike the regulation of drugs, devices, and food additives, the responsibility for safety assessment of cosmetic ingredients and products is the responsibility of the cosmetic ingredient and product manufacturers, not the FDA. Cosmetics do not undergo any premarket approval process at FDA. As a result, it is the cosmetic manufacturer, and/or the cosmetic ingredient manufacturer, that is responsible for assuring that the products sold to the consumers, and the ingredients in those products, are safe for use (*Federal Register* 40(42) March 3, 1975). Moreover, there is no benefit assessment made for cosmetic products. In 1966, Johnson & Johnson was aware that their products were considered to have no health benefit (JNJNL61_000039194). This is consistent with the cosmetic regulatory paradigm that is only based on weighing risks of ingredients and products, not benefits.

107. Manufacturers of cosmetic ingredients and finished cosmetic products have a responsibility to continually monitor the scientific information that develops over time to determine if the risks associated with an ingredient, and/or a product, changes due to things such as previously unknown information, development of additional supporting information that may alter the existing safety profile of a product, and even identification of unanticipated safety concerns that can arise with real world use of products. In other words, the responsibility of the manufacturer does not end once an initial safety determination has been made.

108. As already discussed, the US regulation related to labeling of cosmetics and warnings is as follows (21 CFR 740.1(a)): *"The label of a cosmetic product **shall bear a warning statement** whenever necessary or appropriate **to prevent a health hazard that may be associated with the product**."* This statement means that the standard that must be met when deciding whether to add a warning to the label of a cosmetic warning is whether there is a possibility of a health hazard and that it could be prevented. In the current case, that "possibility" is of cancer occurring in humans using the body powders for genital dusting. The prevention issue would be related to warning consumers not to use the powders for genital dusting. As discussed in detail above, based

on the available scientific data as well as my education, training, and experience, it is my opinion to a reasonable degree of scientific certainty that Imerys and Johnson & Johnson should have initiated actions to add a warning to the labeling of talcum powder products at least by the 1950's that described the adverse health effects linked to talc body powder exposure. Specifically, a warning about serious tissue toxicity and the increased risk of ovarian cancer with use of talcum powder products should have been included on the product labeling. It also is important to note that my earliest report on the safety and regulatory concerns associated with Johnson & Johnson body powder products (dated October 5, 2016) focused on the addition of a specific ovarian cancer warning with genital talc use and discussed the need for a warning by at least 1982. Consistent with these opinions, my reports dated August 29, 2018, November 16, 2018, and June 30, 2021, as well as my deposition and trial testimony in 2018 and 2019, addressed questions raised regarding the need for warnings on Johnson & Johnson talcum body powder products in the period prior to 1982. The basis for my warning opinions is derived from additional review of many internal company documents that pre-dated and post-dated 1982 in conjunction with my review of additional publicly available studies and documents that were dated from the early 1900's through the 1970's.

109. In order to add warnings to a product label in the United States, the company must be aware of the risk, which is why I have outlined what was known and when it was known (discussed above in detail). A review of internal company documents, documents from Johnson & Johnson, Imerys, and the PCPC shows that talc ingredient manufacturers and the manufacturers of talcum powder products were following the published literature and were also intimately involved in the safety assessments of talc over the years (*e.g.,* IMERYS 052752 through 754; P-81; Shripal Sharma deposition dated 9/26/2012; John Hopkins depositions dated 10/26/2012, 8/16/2018 and 8/17/2018; and depositions of Dr. Linda Loretz). Thus, the defendants were at least aware for decades that ovarian cancer *may* be associated with the use of talcum powder products.

110. It is important to note that Johnson & Johnson has undertaken efforts to improve the safety of its products used on babies, which would include its talcum powder products. In 2012, Johnson & Johnson made the decision to remove certain harmful chemicals from its baby products including the IARC Group 2B carcinogen triclosan (see *e.g.,* P-38). This action conflicts with the

company's position on talc, also an IARC 2B carcinogen, where Johnson & Johnson did not include a warning to consumers about the risks associated with genital talc use. Then, in 2018, Johnson and Johnson initiated actions to overhaul its baby product line to be more "natural," by removing artificial ingredients and becoming more transparent in terms of the actual ingredients in its products, including Johnson's Baby Powder. These actions did not lead to removal of talc, or other constituents of its body powder, from its products and their products still failed to provide a warning to consumers about the cancer risk associated with talcum powder products. Instead, by using the word "natural" the companies are now suggesting an improved safety profile despite no substantive changes in the risks linked with the product. It should be noted that at this same time in 2018, other manufacturers of talc-based body powders had already added warnings to the labels of their talc body powder products related to the risk of cancer, even though Johnson & Johnson failed to take such action (*see* Appendix E). In May 2020, Johnson & Johnson stopped distributing its talcum body powder products in the United States and Canada; they did not recall the product from store shelves (see Press Release by Johnson & Johnson dated May 19, 2020)[68]. Existing product continued to be sold. Finally, in August of 2022, Johnson & Johnson announced they would be transitioning to cornstarch globally for all their body powders (see Press Release by Johnson & Johnson dated August 11, 2022).[69]

111. Another action that Johnson & Johnson had taken early on was developing an alternative line of body powders based on the use of cornstarch instead of talc. Johnson & Johnson investigated an alternative body powder product based on cornstarch instead of talc as early as the 1960's (JNJ000265536-538; see Cornstarch Fact Book JNJTALC000864509). Johnson & Johnson filed a patent in 1952 that issued in 1953 for medical dusting powders that were cornstarch-based powders and in that patent identified the significant toxicity associated with talc powders (U.S. Patent 2,626, 257). The text of the patent describes the toxicity of talc in tissue as a reason for finding a replacement. On February 21, 1964, a Johnson & Johnson Memo regarding cornstarch

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[68] https://www.jnj.com/our-company/johnson-johnson-consumer-health-announces-discontinuation-of-talc-based-johnsons-baby-powder-in-u-s-and-canada

[69] https://www.jnj.com/johnson-johnson-consumer-health-to-transition-global-baby-powder-portfolio-to-cornstarch#:~:text=August%2011%2C%202022%20%E2%80%93%20%22As,be%20discontinued%20globally%20in%202023

development states, *"…**it replaced talc because it was found to be absorbed safely in the vagina whereas, of course, talc was not**." [**emphasis** added]* (JNJ000265536-265538) Throughout the 1960's and 1970's, Johnson & Johnson continued to develop cornstarch as a body powder product (*e.g.,* JNJ000265482-483; JNJ000253830-832; JNJ000245901-903; JNJ000245744-748; JNJ000244094-095; JNJ000526750; JNJ000404860; JNJ000279507; JNJ000245762; JNJ000011150; JNJ000026987; JNJ000245678; JNJTALC000866104; JNJ00006987-7007). Important in this process was the fact that the company performed test marketing of a cornstarch Johnson's Baby Powder product in 1977 and found that the cornstarch product *"has been accepted by the consumer as a formula replacement"* (JNJ000245679). In 1978, the FDA's OTC Monograph for skin protectant products (*i.e.,* body powders) listed cornstarch as Generally Recognized as Safe and Effective (GRASE) for use in OTC products (JNJ000470844-846; JNJ000348778) and even noted that cornstarch was recognized as being superior to talc in terms of safety and efficacy (JNJ000470846; JNJ000019415). Therefore, at least by the 1970's, Johnson & Johnson had identified a replacement ingredient for its talcum powder products that they knew was safe and provided the desired cosmetic properties. With respect to the issue of talc as compared to cornstarch powders and ovarian cancer risk, one study has reported that cornstarch is *"not predicted to be a risk factor for ovarian cancer"* (Whysner and Mohan, 2000). With respect to alternative talcum powder products, Imerys has begun work to produce a synthetic talc powder product (Claverie *et al.* 2018; Imerys 2017-2018 Annual Report); such synthetic talc powder should be able to be produced such that it would be free of constituents such as fibrous talc, asbestos, and heavy metals. These actions by Johnson & Johnson as early as the 1950's indicate that the company was aware that there was a safer alternative product, *i.e.,* cornstarch-based body powders, that was also acceptable to their consumers. Yet, it was not until 2022 that Johnson & Johnson took action to replace talc-based body powders entirely with the cornstarch-based products.

112. With respect to Imerys specifically and this issue of warning consumers about risks linked to products, in another internal document (IMERYS 284935 through 937), the importance of the public safety issues surrounding talc, and women's health in particular, were acknowledged by industry. Documents support my opinion that industry was aware of the need to warn consumers of the cancer risk issue in 2006 (P-0033). Yet, no actions were taken to inform the consumer about

the risks associated with talc products. Evidence shows that Imerys began drafting a proposal to FDA wherein industry suggests voluntarily phasing out the production and sale of all cosmetic talc products used for consumer dusting powders that could reasonably be anticipated to be used by women for perineal applications and also to assist the FDA in developing a warning label for body powders containing talc that would warn of the danger of genital dusting (IMERYS 284935 through 937; P-341). Importantly, there is no warning statement on Johnson & Johnson talcum powder products that refers to the risk of cancer of any type, including ovarian cancer with genital dusting.

113. Johnson & Johnson has never placed a warning on its talcum powder products in order to inform consumers about the serious health risks associated with use of their products. The labeling is, and was, inadequate to inform consumers about the risks associated with use of its products, including the risk of cancer. Given that MSDS sheets are not supplied to consumers of talcum powder products, Imerys also failed to ensure that consumers were warned of the risk of cancer associated with genital talc use (IMERYS328096). Placing a warning on the talcum powder product labels would have been an important step towards informing consumers of the hazard associated with repeated use of the products for genital dusting. Given that products were not recalled from consumers, the product may still be in homes, or on the shelves in the United States. Moreover, the labeling for such talc-based powder products fails to warn consumers of the risk of cancer with genital application.

114. In a survey of the commercial market in 2018, I identified several talcum body powder products that have included a consumer warning about an increased risk of cancer. Attached in Appendix E to this report is a series of photographs of bottles of body powder that contained such warnings. For example, some of these product labels state: *"Frequent application of talcum powder in the female genital area may increase the risk of ovarian cancer"*. This is an example of a warning being placed on talc-based body powder products that was consistent with 21 CFR 740.1(a) in the United States.

115. Evidence from other internal corporate documents support my opinions that the defendants were aware that talcum powder products may be associated with a health hazard, which would require a warning on defendants' products. Examples include:

- According to a February 1964 memorandum (P-343), a meeting was held among Johnson & Johnson scientists wherein the issue of talc safety is raised in the context of a discussion of the use of cornstarch as an alternative powder product. The memo stated: *"The largest commercial uses of Dry Flo [a cornstarch powder under development as a talc replacement at J&J] are in Vitamin A manufacture (5% in finished product) and as a condom lubricant where* ***it replaced talc because it was found to be absorbed safely in the vagina whereas, of course, talc was not****." [****emphasis*** *added]*
- In 1966, in response to a publication in the scientific literature (Hughes and Kalmer, 1966), Johnson & Johnson's Dr. Hildick-Smith received a memorandum (JNJNL61_000039194) concerning Johnson's Baby Powder's hazards. Other evidence has shown that Johnson & Johnson routinely followed the published literature related to talc. In the memorandum, the author states *"Baby Powder represents the cornerstone of our baby product franchise. In addition, we have a large investment in a talc mine. I am concerned over the conclusion drawn in the article…"* Importantly, the issue of developing mechanisms to reduce the hazard is raised.
- In a July 9, 1971, memorandum (JNJ000284105-106), Dr. Hildick-Smith memorialized the discussion he had with Dr. Selikoff, an academic scientist who had raised questions with industry about the presence of asbestos in talc. Dr. Selikoff was proposing that a series of studies be carried out, studies that he was willing to perform, to answer critical questions about talc body powder safety.
- In a 1971 internal Johnson & Johnson memorandum (authored by Dr. Hildick-Smith; P-1186), the issue of talc migration from the vagina to the ovaries is discussed. The memorandum describes data that had been collected in women undergoing a hysterectomy where talc placed into the vagina was found to migrate to the ovaries; these data indicate that talc can move inside the body when particles gain entry via the vagina.

- In a March 27, 1972, memorandum (JNJ000468919), Dr. Hildick-Smith confirms that Tenovus Institute would be embarking on a research program to study talc and its relationship to cancer of the ovaries.
- In April of 1972, the National Institute of Occupational Health and Safety (NIOSH) reported that samples of Johnson & Johnson Baby Powder contained significant amounts of fibers (JNJ000260700). The fibers are not specified as being fibrous talc or asbestos. At this point in time, fiber exposure generally was known to pose a risk to human health.
- In a 1973 Johnson & Johnson document (P-1166), key employees discussed the fact that fibrous talc was present in their baby powder as well as the fact that the company could not rely on a "clean mine" approach as a *"a protective device for Baby Powder in the current Asbestos or Asbestos-form controversy."* Defendants were aware that both the talc used to make body powder products and the talc powder products that they produced had fibers in them that were asbestiform in nature and even referred to these as fibrous talc. Also discussed in this document was the fact that one answer to the concerns over the presence of fibers in talc powder products was to replace the talc with cornstarch because *"by its very nature"* it *"does not contain fibers*" and *"it is assimilated by the body"*.
- A January 1974 memorandum (P-660) written by Johnson & Johnson captures the contents of a meeting held on January 16, 1974, with the Commissioner of the FDA regarding data on asbestos in talc that had been brought to the FDA's attention in the early 1970's. In the document Defendants stated: *"If the results of any scientific studies show any question of safety of talc, Johnson & Johnson will not hesitate to take it off the market."* Despite Defendants suggested commitment in the 1970's to actively monitor talc safety issues the company took no action to inform consumers of the potential safety concerns linked to talc body powder.
- A December 3, 1975, Johnson & Johnson memorandum (P-55) is titled *"talc in the ovaries."* Hand-written review notes added by Bruce Semple of Johnson & Johnson raise the question of the company now being *"on notice re: the talc/ovary problem."*

- In a 1986 Johnson & Johnson *"Technological Forecast"* document (P-9), the company admits that there are continuing health concerns with talc and the safety of cosmetic powders, and that the powders have no health benefit.
- A Johnson & Johnson document dated August 5, 1992 (P-10) described declining sales of Baby Powder, including talcum powder products, and the company's desire to grow the powder franchise by targeting minority populations of women; this is a concern given that the same document acknowledges the link of the products with cancer.
- In a document from 1997 written by Johnson & Johnson's own toxicology consultant, Dr. Alfred Wehner, Defendants were informed about false public statements being made by the PCPC regarding talc safety (P-20); yet, Johnson & Johnson did nothing to correct the false impression left by the PCPC's statements.
- In a 1997 document, Johnson & Johnson downplayed the health risks of talc when it responded to media questions about its products (P-115); failing to acknowledge the role that industry played in the 1994 evaluation by FDA and the fact that reliable scientific evidence had raised a signal for cancer risk.
- In a 2000 document from Imerys files, results from a marketing survey discussed that *"the general public is not aware of any health issues regarding talc"* (P-24).
- In a 2000 internal Imerys e-mail, Richard Zazenski, a key Luzenac employee that was involved in responding to the talc safety concerns agrees with the NTP reviewers that the epidemiology studies are concerning, and the data is not dismissible. The e-mail also suggested that he may even agree with adding warning labels (IMERYS 240341).
- A 2000 memorandum prepared by Burson-Marsteller for Johnson & Johnson announced the intent to only use cornstarch beginning December 1, 2000, and discontinue the use of talc in all consumer products (JNJ000404424 and JNJ000404425). Despite their marketing piece, Johnson & Johnson continued to use talc in their consumer body powder products for more than two decades (up until 2022).
- In a 2001 presentation by Steve Jarvis of Imerys, the adverse human health effects of talc are acknowledged. He states that "*there are some health issues with talc"*

based on finding for 20 years a "*persistent statistical link between the hygienic use of talc and ovarian cancer*" (IMERYS 178944).

- In a January 2, 2001 e-mail (P-317) from Rich Zazenski to Eric Turner (both employees of Luzenac, now known as Imerys), the two men discussed the NTP's 2000 RoC process and how the *industry "dodged a bullet in December based entirely on the confusion over the definition issue"*, where the definition issue referred to the purity of talc that would have been used by women involved in the older epidemiology studies where asbestos was more likely to have been found in cosmetic talc products. The discussion went on to describe how this issue may be addressed by NTP such that cosmetic grade talc would be listed in the future as having limited evidence from human studies, a standard that would likely lead to a NTP listing of talc in the RoC. Thus, Defendants were aware of the human health hazards that had been linked to talc exposure through use of talc body powders.
- In a February 26, 2002, document (P-26), Mr. Zazenski described an outcome if talc without asbestiform fibers were to be listed as a carcinogen by NTP. The document addresses the issues surrounding the need to warn consumers about the cancer issue.
- In a series of e-mails in January 2005 (JNJ000390337-339), Johnson & Johnson employees discussed the fact that talc body powder product Material Safety Data Sheets (MSDSs) should include a listing for talc as a component(s) that "have been defined as a cancer-suspect agent by worldwide reputable agency". Yet, in the same e-mail chain the response from another Johnson & Johnson employee was*: "Do NOT send out any MSDS with this statement on it!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!" [the large number of exclamation points is in the document itself at JNJ000390337]*
- In 2006, Imerys changed their talc Material Safety Data Sheet (MSDS) to add that IARC had listed talc body powders as "possibly" carcinogenic to humans (IMERYS 188701-705) yet consumers were not provided the same information on product labeling.

- In a 2008 email Todd True, former Global Creative Director for Johnson & Johnson, Mr. True said: *"The reality that* ***talc is unsafe*** *for use on/around babies is disturbing. I don't mind selling talc, I just don't think we can continue to call it Baby Powder and keep it in the baby aisle."* Fred Koberna, another Johnson & Johnson employee, responds, *"My understanding is that we introduced the cornstarch variant as an alternative to talc for use on babies. Due to the talc issue and some doctors recommending for moms not use powder on their babies, we don't promote powder to moms."* Mr. True responded, *"I am on a bit of a mission to strongly consider removing talc from the baby aisle."* (JNJ000457161) *[**emphasis** added]*
- In a 2009 memo, Imerys criticized Johnson & Johnson for preferring to purchase talc based on cost rather than quality (P-560)
- In 2010, Johnson & Johnson made media recommendations for advertising its talc body powder products (P-374). In the document, Defendant discussed a key strategy and tactic to be *"target overweight women living in hot climates during key summery season"*. This recommendation was made despite evidence that the cosmetic warning standard for a possible human health hazard had been met for talcum powder.
- In two documents related to Johnson & Johnson's pharmacovigilance assessments in 2012 through 2014 (P-882 and P-883), employees had determined there was a causal connection between talc body powder use and certain cases of ovarian cancer reported to the company, but the decision was made to remove the language about causality from the records for those cases.

116. Documents in company files also reveal that in November 1994, Johnson & Johnson received a letter from Dr. Samuel Epstein, chairman of the group known as the Cancer Prevention Coalition (P-18), notifying the CEO of Johnson & Johnson of the filing of the Citizens' Petition. In that letter, Dr. Epstein requested that talc products be withdrawn from the market due to the concern with human cancer, or that, at least, a label warning should be required for consumers regarding the concerns of ovarian cancer with talc use. Fifteen years later, in 2009, the PCPC filed comments on behalf of industry to this 1994 Citizen's Petition; the same group filed a

second Citizen's Petition in 2008 because of developing science in the area and the fact that FDA had failed to respond to the original petition filed in 1994. Although industry disagreed with Dr. Epstein's position, it agreed that reasonable scientists looking at the data could disagree with industry, that this disagreement was one that was expressed by responsible scientists over decades, and that defendants could voluntarily change the label without being required to do so by the FDA. Yet, Johnson & Johnson did not warn about the risk of cancer following receipt of their letter in 1994. Given the expertise of Dr. Epstein and the fact that he was pointing to reliable scientific information to support his concerns, Johnson & Johnson had a duty to inform consumers of the potential risks associated with talc use, particularly in women using body powders for genital application.

117. Other industry actions related to talc and the safe use of talc powders in humans that inform my opinions and warrant discussion include the removal of talc powder as a lubricant for condoms and for surgical gloves. With respect to use of talc powder on condoms, manufacturers decided in 1996 to no longer use talc on condoms (IMERYS-A_0011817; 16 January 1996 article in Asbury Park Press; P-0019). The decision was driven in part by the opinions expressed by scientists in the published literature concerning the health hazards associated with talc (Kang *et al.* 1992; Kasper and Chandler, 1995). Talc industry members such as Johnson & Johnson, Imerys and the PCPC were aware of these actions (PCPC_MDL00062175; PCPC0075758). With respect to use of talc powders on surgical gloves, the risks to human health had been recognized in the 1950's (discussed above). In 2016, FDA acted to formally ban use of powders, including talc, on surgical gloves (*Federal Register* December 16, 2016).[70]

118. Documents show that, instead of providing consumers with warnings and safety information regarding use of talcum powder products, industry performed marketing research (*e.g.,* PCPC0077761-77926; P-24). From the results of the market research, industry knew that consumers were unaware of the safety concerns associated with use of talc-based body powders in the genital area. Importantly, during the process of collecting the consumer data, consumers

[70] It is important to realize that the group at FDA that banned the use in 2016 was the FDA's Center for Devices and Radiological Health (CDRH) which had very different regulatory authority at the time in 2016 (https://www.govinfo.gov/content/pkg/FR-1998-02-02/pdf/98-2498.pdf) as compared to the Office of Cosmetics within the FDA's Center for Food Safety and Nutrition (CFSAN).

participating were told that the information on the link of talc use with cancer was "hypothetical", even though industry was aware of a wide variety of scientific data where well-respected scientists had concluded that talc posed a cancer hazard to humans. Evidence shows industry also marketed talcum body powders by targeting populations with a known propensity to use talc body powders in the genital area (P-10; P-0374; P-771).

119. Documents show that Defendants recognized the health hazard of talcum powder products and the potential consequences of failing to inform the scientific and medical community, regulators, and consumers of those hazards (P-26; P-27; P-66). They even developed a document discussing questioning around the safety issue. The document shows that industry understood that data existed supporting the safety concerns.

IX. Conclusions

120. In conclusion, based on my training and experience in pharmacology, toxicology, pharmacokinetics, human health risk assessment, and the regulation of cosmetic products in the United States, it is my opinion to a reasonable degree of scientific certainty that the weight-of-the-evidence indicates that genital exposure to talcum powder products increases the risk of ovarian cancer in women. This conclusion is supported by data that includes, but is not limited to the following: (1) the known toxic effects of talc and the other components of talcum powder products; (2) studies that have identified biologically plausible mechanisms for cancer in humans; (3) the likelihood that talc particles can reach the ovaries; (4) the existence of a dose-response relationship for toxicity including the risk of cancer; and (5) the large human database that includes studies conducted over a period of 40 years showing a consistent signal for ovarian cancer in women exposed to talcum powder products.

121. It is also my opinion to a reasonable degree of scientific certainty that the use of talc in cosmetic products does not meet the CIR standard of safety. Given the presence of asbestos, fibrous talc, cobalt, chromium, and nickel, in the talc body powders manufactured by Imerys and Johnson & Johnson, a significant biologically plausible human health risk was identified as a hazard related to talc body powder use at least by the 1940's. These risks included a risk of cancer with exposure to constituents of talc body powders, and even death with acute inhalation of large

amounts of the powder. Based on the knowledge available by the 1950's, talc body powders manufactured and sold by Imerys and Johnson & Johnson should have warned consumers about the toxic constituents, such as asbestos, fibrous talc, nickel, chromium and cobalt and fragrance, in their products and the effects that could be produced by exposure to talc dusts. There was evidence from at least the 1960's of the risk of ovarian cancer in women exposed to components of talc body powders, evidence that has only gained strength over the last six decades. The CIR standard states that there is *"no evidence"* that demonstrates grounds to suspect a hazard to the public under conditions of use. Failure to meet the CIR standard for safety meant that Johnson & Johnson failed to properly substantiate and ensure the safety of their cosmetic body powder products. Given that Johnson & Johnson was aware that cornstarch-based body powder products represented a safer alternative, their failure to replace talc with cornstarch over the years that they marketed talc-based body powders put consumer health at risk.

122. Based upon my review of the scientific evidence, it also is my opinion within a reasonable degree of scientific certainty that talc-based cosmetic products, including products used by women for genital dusting, should have been labeled to warn of the risk of ovarian cancer with such use. This specific ovarian cancer risk was evident by the 1960's given the presence of asbestos in talc body powders. This opinion is based on the FDA regulations that state that *"the label of a cosmetic product shall bear a warning statement whenever necessary or appropriate to prevent a health hazard that may be associated with the product"* (21 CFR 740.1(a)). It is important to note that cause and effect do not have to be proven for such a warning to be put into place. Given that Defendants have never placed an adequate warning onto its containers of talcum powder products, the failure to provide consumers with such information puts public health at risk.

123. In addition to failing to warn consumers about the serious health risks that had been linked to genital use of talc, where evidence had been accumulating for decades, the presence of carcinogenic constituents in talc such as asbestos, fibrous talc, nickel, chromium, and cobalt meant that Johnson & Johnson's failure to list those talc constituents on its labeling was consistent with the FDA's definition of a misbranded product, and also consistent with the FDA's definition of an adulterated product.

124. Finally, it is my opinion to a reasonable degree of scientific certainty that rather than perform studies to address talc safety concerns that arose over the years, or provide consumers with complete and timely safety information about the human health risks of talc when it was used for genital dusting, industry worked together with the PCPC to influence the scientific and regulatory processes related to cosmetic talcum powder products such that the scientific and medical communities, as well as consumers, were not provided with important safety information about use of the products.

125. I hereby certify that this report is a complete and accurate statement of all my opinions, and the basis and reasons for them, to which I will testify under oath.

X. Compensation

126. My compensation for litigation work, for both defense attorneys and plaintiff attorneys, is at the rate of $300.00 per hour.

REFERENCES

Abraham, J.L. and D.D. McEuen. 1986. Inorganic particulates associated with pulmonary alveolar proteinosis: SEM and X-ray microanalysis results. *Appl. Pathol.* 4(3):138-146.

Acheson, E.D. *et al.* 1982. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *Br. J. Ind. Med.* 39(4):344-348.

Adamson, I.Y. and H. Prieditis. 1998. Silica deposition in the lung during epithelial injury potentiates fibrosis and increases particle translocation to lymph nodes. *Exp. Lung Res.* 24(3):293-306.

Agency for Toxic Substances and Disease Registry (ATSDR). 2001. *Toxicological profile for asbestos*. Agency for Toxic Substances and Disease Registry, Division of Toxicology/Toxicology Information Branch.

Alexander, N.J. *et al.* 2004. Why consider vaginal drug administration? *Fertil. Steril*. 82(1):1-12.

Anderson, E.L. *et al.* 2017. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. *Risk Anal.* 37(5):918-929.

Arellano-Orden, E. *et al.* 2013. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. *Respiration* 86(3):201-209.

Axelson, O. *et al.* 2003. Re: Regulatory Toxicology and Pharmacology. *Int. J. Occup. Environ. Health* 9(4):386-389.

Beck, B.D. *et al.* 1987. The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay. *Toxicol. Appl. Pharmacol.* 87(2):222-234.

Berge, W. *et al.* 2018. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur. J. Cancer Prev.* 27(3):248-257.

Berger, M. and Berger, B.A. 2017. FDA and related regulatory agencies. In: *Fundamentals of US Regulatory Affairs*, *10th edition*. P.A. Jones, Senior Editor, Regulatory Affairs Professionals Society: Rockville, MD, chapter 1.

Blejer, H.P. and R. Arlon. 1973. Talc: a possible occupational and environmental carcinogen. *J. Occup. Med.* 15(2):92-97.

Blount, A.M. 1991. Amphibole content of cosmetic and pharmaceutical talcs. *Environ. Health Perspect.* 94:225-230.

Bluemel, G., F. Piza, and W. Zischka-Konorsa. 1962. [Experimental animal research on the tissue reaction to starch and talc powder after their intraperitoneal use]. *Wien. Klin. Wochenschr.* 74:12-13.

Blumenkrantz, M.J. *et al.* 1981. Retrograde menstruation in women undergoing chronic peritoneal dialysis. *Obstet. Gynecol.* 57(5):667-670.

Boorman, G.A. and J.C. Seeley. 1995. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. *Regul. Toxicol. Pharmacol*. 21:242-243.

Booth, M., V. Beral, and P. Smith. 1989. Risk factors for ovarian cancer: a case-control study. *Br. J. Cancer* 60(4):592-598.

Brouillette, F. and M.L. Weber. 1978. Massive aspiration of talcum powder by an infant. *Can. Med. Assoc. J.* 119(4):354-355.

Bulbulyan, M.A. *et al.* 1999. Cancer mortality among women in the Russian printing industry. *Am. J. Ind. Med.* 36(1):166-171.

Bunderson-Schelvan, M. *et al.* 2011. Nonpulmonary outcomes of asbestos exposure. *J. Toxicol. Environ. Health B Crit. Rev.* 14(1-4):122-152.

Buz'Zard, A.R. and B.H. Lau. 2007. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytother. Res.* 21(6):579-586.

Camargo, M.C. *et al.* 2011. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ. Health Perspect.* 119(9):1211-1217.

Carr, C.J. 1995. Talc: Consumer uses and health perspectives. *Regul. Toxicol. Pharmacol.* 21:211-215.

Chang, S. and H.A. Risch. 1997. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 79(12):2396-2401.

Chen, Y. *et al.* 1992. Risk factors for epithelial ovarian cancer in Beijing, China. *Int. J. Epidemiol.* 21(1):23-29.

Claverie, M. *et al.* 2018. Synthetic talc and talc-like structures: preparation, features and applications. *Chemistry* 24 (3):519-542.

Cosmetic Ingredient Review (CIR). 2013. *Safety assessment of talc as used in cosmetics*. Final report dated April 12, 2013. Panel meeting date: March 18-19, 2013.

Cless, D. and R. Anger. 1954. [Fatal asphyxia caused by aspiration of baby powder]. *Kinderarztl. Prax.* 22(11):506-508.

Congressional Research Service (CRS). 7-29-2012. *FDA regulation of cosmetics and personal care products*.

Cook, L.S., M.L. Kamb, and N.S. Weiss. 1997. Perineal powder exposure and the risk of ovarian cancer. *Am. J. Epidemiol.* 145(5):459-465.

Cooke, W.E. 1927. Pulmonary Asbestosis. *Br. Med. J.* 2(3491):1024-1025.

Cosmetic Ingredient Review (CIR). 2013. Safety Assessment of Talc As Used in Cosmetics. Status: Final Report. Release Date: April 12, 2013. Panel Meeting Date: March 18-19, 2013 *[https://www.cir-safety.org/sites/default/files/talc032013rep.pdf]*

Cralley, L.J. *et al.* 1968. Fibrous and mineral content of cosmetic talcum products. *Am. Ind. Hyg. Assoc J.* 29(4):350-354.

Cramer, D.W. *et al.* 1982. Ovarian cancer and talc: a case-control study. *Cancer* 50(2):372-376.

Cramer, D. and H. Xu. 1995. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. *Ann. Epidemiol.* 5(4):310-314.

Cramer, D.W. *et al.* 1999. Genital talc exposure and risk of ovarian cancer. *Int. J. Cancer* 81(3):351-356.

Cramer, D.W. 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet. Gynecol.* 94(1):160-161.

Cramer, D.W. *et al.* 2007. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet. Gynecol.* 110(2 Pt 2):498-501.

Cramer, D.W. *et al.* 2016. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. *Epidemiology* 27(3):334-346.

Creery, R.D., D.M. McClure, and R.J. Rutherford. 1957. Talc granuloma of the umbilicus. *Lancet* 272(6970):667-668.

Daly, M. and G.I. Obrams. 1998. Epidemiology and risk assessment for ovarian cancer. *Semin. Oncol.* 25(3):255-264.

Davies, R. *et al.* 1983. Cytotoxicity of talc for macrophages in vitro. *Food Chem. Toxicol.* 21(2):201-207.

Davis, C.P. *et al.* 2021. Genital powder use and risk of epithelial ovarian cancer in the Ovarian Cancer in Women of African Ancestry Consortium. *Cancer Epidemiol. Biomarkers Prev.* 30:1660–1668.

De Boer, C.H. 1972. Transport of particulate matter through the human female genital tract. *J. Reprod. Fertil.* 28(2):295-297.

Ding, D-N. *et al.* 2021. Insights into the role of oxidative stress in ovarian cancer. *Oxid. Med. Cell Longev.* Oct 7:8388258.

Doll, R. 1955. Mortality from lung cancer in asbestos workers. *Br. J. Ind. Med.* 12(2):81-86.

Dreessen, W.C. 1933. Effects of certain silicate dusts on the lungs. *J. Ind. Hyg.* 15:66-78.

Dreessen, W.C. and J.M. Dalla Valle. 1935. The effects of exposure to dust in two Georgia talc mills and mines. *Pub. Health Rep.* 50(5):131-143.

Eaton, D.L. and S.G. Gilbert. 2013. Principles of toxicology. In: *Casarett and Doull's Toxicology, The Basic Science of Poisons*, *8th edition*. C.D. Klaassen (ed.), The McGraw-Hill Education: New York, NY, chapter 2.

Eberl, J.J. *et al.* 1948. Comparative evaluation of the effects of talcum and a new absorbable substitute on surgical gloves. *Am. J. Surg.* 75(3):493-497.

Edelstam, G.A., A.C. Sjosten, and H. Ellis. 1997. Retrograde migration of starch in the genital tract of rabbits. *Inflammation* 21(5):489-499.

Egilman, D. and J. Steffen. 2018. Commentary on "Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder". *New Solut.* 28(3):400-409.

Egli, G.E. and M. Newton. 1961. The transport of carbon particles in the human female reproductive tract. *Fertil. Steril.* 12:151-155.

Eiseman, B., M.G. Seelig, and N.A. Womack. 1947. Talcum powder granuloma: a frequent and serious postoperative complication. *Ann. Surg.* 126(5):820-832.

Eltabbakh, G.H. *et al.* 1998. Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. *Obstet. Gynecol.* 91(2):254-259.

Emi, T. *et al.* 2021. Transcriptomic and epigenomic effects of insoluble particles on J774 macrophages. *Epigenetics* 16(10):1053-1070

United States Environmental Protection Agency (EPA). 1986. *Health Effects Assessment for Asbestos*. [https://nepis.epa.gov/Exe/ZyPDF.cgi/2000DAJA.PDF?Dockey=2000DAJA.PDF]

United States Environmental Protection Agency (EPA). 1986. *Guidelines for Mutagenicity Risk Assessment.* [*https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23160&CFID=65932199&CFTOKEN=24176705]*

United States Environmental Protection Agency (EPA). 1992. *Health Assessment Document for Talc.* Office of Research and Development. [https://nepis.epa.gov/Exe/ZyPDF.cgi/30001O5C.PDF?Dockey=30001O5C.PDF]

United States Environmental Protection Agency (EPA). 1994. *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry.* [*https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=65932266&CFTOKEN=97071893*]

United States Environmental Protection Agency (EPA). 2000. *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*. USEPA Risk Assessment Forum. *[https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533]*

United States Environmental Protection Agency (EPA). 2015. EDSP: Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen or Thyroid Pathways. Chemical: Acephate. [*https://www.epa.gov/sites/production/files/2015-06/documents/acephate-103301_2015-06-29_txr0057153.pdf]*

United States Food and Drug Administration (FDA). 1997. *Guidance for Industry: S1B Testing for Carcinogenicity of Pharmaceuticals.* [*http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf*]

United States Food and Drug Administration (FDA). 2006. *Guidance for Industry and Review Staff: Recommended Approaches to Integration of Genetic Toxicology Study Results.* [*http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079257.pdf]*

United States Food and Drug Administration (FDA). 2011. *Guidance for Industry: Reproductive and Developmental Toxicities - Integrating Study Results to Assess Concerns*. [*http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079240.pdf*]

United States Food and Drug Administration (FDA). 2014. *Talc.* [*http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm*]

United States Food and Drug Administration (FDA). 2016. *How FDA Evaluates Regulated Products: Cosmetics.* [*http://www.fda.gov/aboutfda/transparency/basics/ucm262353.htm]*

United States Food and Drug Administration (FDA). 2016. *Food and Drug Administration: Cosmetic Labeling Guide.* [*http://www.fda.gov/downloads/Cosmetics/Labeling/UCM391202.pdf]*

United States Food and Drug Administration (FDA). 2016. *Draft Guidance for Industry: Cosmetic Good Manufacturing Practices.* [*http://www.fda.gov/cosmetics/guidanceregulation/guidancedocuments/ucm353046.htm]*

United States Food and Drug Administration (FDA). 2016. *FDA Authority Over Cosmetics: How Cosmetics Are Not FDA-Approved, But Are FDA-Regulated.* [*http://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074162.htm*]

Fernandes, J.V. *et al.* 2015. The role of the mediators of inflammation in cancer development. *Pathol. Oncol. Res.* 21(3):527-534.

Ferrante, D. *et al.* 2017. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. *Occup. Environ. Med.* 74(12):887-898.

Fiume, M.M. *et al.* 2015. Safety assessment of talc as used in cosmetics. *Int. J. Toxicol* 34(1 Suppl):66S-129S.

Fleming, J.S. *et al.* 2006. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. *Mol. Cell. Endocrinol.* 247(1-2):4-21.

Fletcher, N.M. and G.M. Saed. 2018. Talcum powder enhances cancer antigen 125 levels in ovarian cancer cells. Presented at the 65th Meeting of the Society for Reproductive Investigation, San Diego, California.

Fletcher, N.M. *et al.* 2018. Talcum powder enhances oxidative stress in ovarian cancer cells. *Reprod. Sci.* 25(Supplement 1):214A-215A.

Fletcher, N.M. *et al.* 2019. Molecular basis supporting the association of talcum powder use with increased risk of ovarian cancer. *Reprod Sci.* 26(12):1603-1612.

Frank, C. and L. Jorge. 2011. An uncommon hazard: Pulmonary talcosis as a result of recurrent aspiration of baby powder. *Respir. Med. CME* 4:109-111.

Fubini, B. and I. Fenoglio. 2007. Toxic potential of mineral dusts. *Elements* 3:407-414.

Gardner, D. L., Fink, D. J., and Hassler, C. R. 1981. Potential delivery of contraceptive agents to the female reproductive tract. In: *Controlled Release of Pesticides and Pharmaceuticals*. D.H. Lewis, Southern Research Institute: Birmingham, AL, chapter 8.

Germani, D. *et al.* 1999. Cohort mortality study of women compensated for asbestosis in Italy. *Am. J. Ind. Med.* 36(1):129-134.

Gertig, D.M. *et al.* 2000. Prospective study of talc use and ovarian cancer. *J. Natl. Cancer Inst.* 92(3):249-252.

Gloyne, S.R. 1935. Two cases of squamous carcinoma of the lung occurring in asbestosis. *Tubercle* 17(1):5-10.

Godard, B. *et al.* 1998. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am. J. Obstet. Gynecol.* 179(2):403-410.

Gondal, M.A. *et al.* 2012. Detection of toxic metals (lead and chromium) in talcum powder using laser induced breakdown spectroscopy. *Appl. Opt.* 51(30):7395-7401.

Gordon, R.E., S. Fitzgerald, and J. Millette. 2014. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. *Int. J. Occup. Environ. Health* 20(4):318-332.

Government Accounting Office (GAO). 1978. *Lack of authority hampers attempts to increase cosmetic safety.* United States General Accounting Office.

Graham, J. and R. Graham. 1967. Ovarian cancer and asbestos. *Environ. Res.* 1(2):115-128.

Graham, J.D. and M.E. Jenkins. 1952. Value of modified starch as a substitute for talc. *Lancet* 1(6708):590-591.

Green, A. *et al.* 1997. Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. *Int. J. Cancer* 71(6):948-951.

Greenburg, L. 1947. The dust hazard in tremolite talc mining. *Yale J. Biol. Med.* 19(4):481-501.

Grivennikov, S.I., F.R. Greten, and M. Karin. 2010. Immunity, inflammation, and cancer. *Cell* 140(6):883-899.

Halme, J. *et al.* 1984. Retrograde menstruation in healthy women and in patients with endometriosis. *Obstet. Gynecol.* 64(2):151-154.

Hamilton, J.A., G. McCarthy, and G. Whitty. 2001. Inflammatory microcrystals induce murine macrophage survival and DNA synthesis. *Arthritis Res.* 3(4):242-246.

Hamilton, T.C. *et al.* 1984. Effects of talc on the rat ovary. *Br. J. Exp. Pathol.* 65(1):101-106.

Harlow, B.L. and N.S. Weiss. 1989. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. *Am. J. Epidemiol.* 130(2):390-394.

Harlow, B.L. *et al.* 1992. Perineal exposure to talc and ovarian cancer risk. *Obstet. Gynecol.* 80(1):19-26.

Harper, A.K. *et al.* 2023. Talcum powder induces malignant transformation in normal human primary ovarian epithelial cells. *Minerva Obstet. Gynecol.* 75(2):150-157.

Hartge, P. *et al.* 1983. Talc and ovarian cancer. *JAMA* 250(14):1844

Health Canada. 2021. Screening Assessment: Talc (Mg3H2(SiO3)4). Chemical Abstracts Service Registry Number 14807-96-6. Environment and Climate Change Canada and Health Canada. April. *[https://www.canada.ca/en/environment-climate-change/services/evaluating-existing-substances/screening-assessment-talc.html]*

Heller, D.S. *et al.* 1996. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am. J. Obstet. Gynecol.* 174(5):1507-1510.

Henderson, W.J. *et al.* 1971. Talc and carcinoma of the ovary and cervix. *J. Obstet. Gynaecol. Br. Common.* 78(3):266-272.

Henderson, W.J., T.C. Hamilton, and K. Griffiths. 1979. Talc in normal and malignant ovarian tissue. *Lancet* 1(8114):499

Henderson, W.J. *et al.* 1986. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. *Environ. Res.* 40(2):247-250.

Hildick-Smith, G.Y. 1976. The biology of talc. *Br. J. Ind. Med.* 33(4):217-229.

Hillegass, J.M. *et al.* 2010. Utilization of gene profiling and proteomics to determine mineral pathogenicity in a human mesothelial cell line (LP9/TERT-1). *J. Toxicol. Environ. Health A* 73(5):423-436.

Hogue, W.L., Jr. and F.S. Mallette. 1949. A study of workers exposed to talc and other dusting compounds in the rubber industry. *J. Ind. Hyg. Toxicol.* 31(6):359-364.

Houghton, S.C. *et al.* 2014. Perineal powder use and risk of ovarian cancer. *J. Natl. Cancer Inst.* 106(9).

Hourihane, D.O. and W.T. McCaughey. 1966. Pathological aspects of asbestosis. *Postgrad. Med. J.* 42(492):613-622.

Hughes, W.T. and T. Kalmer. 1966. Massive talc aspiration. Successful treatment with dexamethasone. *Amer. J. Dis. Child.* 111:653-654.

Huncharek, M., J.F. Geschwind, and B. Kupelnick. 2003. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res.* 23(2C):1955-1960.

Huncharek, M. *et al.* 2007. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. *Eur. J. Cancer Prev.* 16(5):422-429.

Huncharek, M. and J. Muscat. 2011. Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology. *Eur. J. Cancer Prev.* 20(6):501-507.

International Agency for Research on Cancer (IARC). 1987. *IARC Monographs on the evaluations of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs Volumes 1 to 42*. World Health Organization International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 1997. *IARC Working Group on the Evaluation of Carcinogenic Risks to Humans: Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils.* 68:1-475.

International Agency for Research on Cancer (IARC). 2006. *IARC Monographs on the evaluations of carcinogenic risks to humans. Preamble*. World Health Organization International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2010. *IARC Monographs on the evaluations of carcinogenic risks to humans. Carbon black, titanium dioxide and talc.* World Health Organization International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2012. *IARC Monographs on the evaluations of carcinogenic risks to humans. Arsenic, metals, fibres and dusts. A review of human carcinogens*. World Health Organization International Agency for Research on Cancer.

Iturralde, M. and P.F. Venter. 1981. Hysterosalpingo-radionuclide scintigraphy (HERS). *Semin. Nucl. Med.* 11(4):301-314.

Jackson, E.M. 1995. Consumer products: Cosmetics and topical over-the-counter drug products. In: *Regulatory Toxicology*. C.P. Chengelis et al. (eds.), Raven Press, Ltd.: New York, chapter 5.

Jaques, W.E. and K. Benirschke. 1952. Pulmonary talcosis with involvement of the stomach and the heart; report of a case. *AMA. Arch. Ind. Hyg. Occup. Med.* 5(5):451-463.

Jasuja, S. *et al.* 2017. Cosmetic talc-related pulmonary granulomatosis. *J. Invest. Med. High Impact. Case. Rep.* 5(3):2324709617728527

Jenkins, M.Q. 1963. Poisoning of the month. Dusting powder inhalation. *J. S.C. Med. Assoc.* 59:62.

Johnson, K.E. *et al.* 2020. Analytic comparison of talc in commercially available baby powder and in pelvic tissues resected from ovarian carcinoma patients. *Gynecol. Oncol.* 159(2):527-553.

Jordan, S.J. *et al.* 2007. Risk factors for benign serous and mucinous epithelial ovarian tumors. *Obstet. Gynecol.* 109(3):647-654.

Kadanali, S. *et al.* 2001. Evaluation of active and passive transport mechanisms in genital tracts of IUD-bearing women with radionuclide hysterosalpingoscintigraphy. *Contraception* 63(1):41-45.

Kaiser, W. *et al.* 1982. [Unspecific tissue reactions caused by glove powder]. *Fortschr. Med.* 100(25):1213-1216.

Kamp, D.W., E. Shacter, and S.A. Weitzman. 2011. Chronic inflammation and cancer: the role of the mitochondria. *Oncology (Williston.Park)* 25(5):400-10, 413.

Kang, N., D. Griffin, and H. Ellis. 1992. The pathological effects of glove and condom dusting powders. *J. Appl. Toxicol.* 12(6):443-449.

Kasper, C.S. and P.J. Chandler, Jr. 1995. Possible morbidity in women from talc on condoms. *JAMA* 273(11):846-847.

Keal, E.E. 1960. Asbestosis and abdominal neoplasms. *Lancet* 2(7162):1211-1216.

Kennedy, D. 1978. The Food and Drug Administration and the backward motion toward the source. *Public Health Rep.* 93(6):607-615.

Kim, S.Y. *et al.* 2024. Asbestos exposure and ovarian cancer: a meta-analysis. *Saf. Health Work* 15:1-8.

Kissler, S. *et al.* 2004. Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement. *Acta Obstet. Gynecol. Scand.* 83(4):369-374.

Klaunig, J.E. 2013. Chemical carcinogenesis. In: *Casarett and Doull's Toxicology, The Basic Science of Poisons*, *8th edition*. C.D. Klaassen (ed), The McGraw-Hill Companies, Inc.: New York, NY, chapter 8.

Kleinfeld, M., J. Messite, and I. R. Tabershaw. 1955. Talc pneumoconiosis. *AMA Arch. Ind. Health* 12(1):66-72.

Kleinfeld, M. *et al.* 1963. Talc pneumoconiosis: a report of six patients with postmortem findings. *Arch. Environ. Health* 7:101-115.

Kleinfeld, M. *et al.* 1964. Lung function in talc workers. *Arch Environ. Health* 9:559-566.

Kleinfeld, M. *et al.* 1967. Mortality among talc miners and millers in New York State. *Arch. Environ. Health* 14(5):663-667.

Kleinfeld, M., J. Messite, and A.M. Langer. 1973. A study of workers exposed to asbestiform minerals in commercial talc manufacture. *Environ. Res.* 6(2):132-143.

Kunz, G. *et al.* 1996. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. *Hum. Reprod.* 11(3):627-632.

Kunz, G. *et al.* 1997. The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. *Adv. Exp. Med. Biol.* 424:267-277.

Kunz, G. and G. Leyendecker. 2002. Uterine peristaltic activity during the menstrual cycle: characterization, regulation, function and dysfunction. *Reprod. Biomed. Online* 4 Suppl 3:5-9.

Kunz, G. *et al.* 2007. Oxytocin--a stimulator of directed sperm transport in humans. *Reprod. Biomed. Online* 14(1):32-39.

Kupryjanczyk, J. 1989. Adenomatoid tumour of the ovary and uterus in the same patient. *Zentralbl. Allg. Pathol.* 135(5):437-444.

Kurta, M.L. *et al.* 2012. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol. Biomarkers Prev.* 21(8):1282-1292.

Landskron, G. *et al.* 2014. Chronic inflammation and cytokines in the tumor microenvironment. *J. Immunol. Res.*14:1-19.

Langseth, H. and K. Kjaerheim. 2004. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scand. J. Work. Environ. Health* 30(5):356-361.

Lauchlan, S.C. 1994. The secondary Mullerian system revisited. *Int. J. Gynecol. Pathol*. 13:73-79.

Leak, L.V. 1980. Lymphatic removal of fluids and particles in the mammalian lung. *Environ. Health Perspect.* 35:55-75.

Longo, D.L. and R.C. Young. 1979. Cosmetic talc and ovarian cancer. *Lancet* 2(8138):349-351.

Lu, H., W. Ouyang, and C. Huang. 2006. Inflammation, a key event in cancer development. *Mol. Cancer Res.* 4(4):221-233.

Magnani, C. *et al.* 2008. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup. Environ. Med.* 65(3):164-170.

Mandarino, A. *et al.* 2020. The effect of talc particles on phagocytes in co-culture with ovarian cancer cells. *Environ. Res.* 120:108676.

Mann, B. and J.B. Deasy. 1954. Talc pneumoconiosis in the textile industry. *Br. Med. J.* 2(4902):1460-1461.

Mattenklott, M. 2007. Asbestos in talcum powders and soapstone - the present state (TRANSLATION). *Gefahrstoffe Reinhaltung der Luft* 67((7-8)):287-291.

McCalley, M.G. *et al.* 1985. Radionuclide hysterosalpingography for evaluation of fallopian tube patency. *J. Nucl. Med.* 26(8):868-874.

McDonald, S.A. *et al.* 2019a. Migration of talc from the perineum to multiple pelvic organ sites: five case studies with correlative light and scanning electron microscopy. *Am. J. Clin. Pathol.* 152:590-607.

McDonald, S.A. *et al.* 2019b. Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes. *Ultrastruc. Pathol.* 43(1):13-27.

McLaughlin, A.I., E. Rogers, and K. C. Dunham. 1949. Talc pneumoconiosis. *Br. J. Ind. Med.* 6(3):184-194.

Merewether, E.R.A. and C.W. Price 1930. *Report on effects of asbestos dust on the lungs and dust suppression in the asbestos industry*. His Majesty's Stationery Office.

Merewether, E.R.A. 1930. The occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers. *J. Ind. Hyg.* 12:198-222, 239-257.

Merliss, R.R. 1971. Talc-treated rice and Japanese stomach cancer. *Science* 173(4002):1141-1142.

Merritt, M.A. *et al.* 2008. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int. J. Cancer* 122(1):170-176.

Michaels, D. 2008. *Doubt Is Their Product. How Industry's Assault on Science Threatens Your Health.* Oxford University Press, Inc.: New York, NY.

Michaels, D. 2020. *The Triumph of Doubt. Dark Money and the Science of Deception.* Oxford University Press, Inc.: New York, NY.

Migaki, G. and F.M. Garner. 1969. Talc-induced granulomas in swine. *J. Am. Vet. Med. Assoc.* 155(10):1595-1596.

Miller, A. *et al.* 1971. Talc pneumoconiosis. Significance of sublight microscopic mineral particles. *Am. J. Med.* 50(3):395-402.

Miller, J.W. and R.R. Sayers. 1936. The physiological response of peritoneal tissue to certain industrial and pure mineral dusts. *Pub. Health Rep.* 51(49):1677-1689.

Millman, N. 1947. Pneumoconiosis due to talc in the cosmetic industry. *Occup. Med.* 4(4):391-394.

Mills, P.K. *et al.* 2004. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. *Int. J. Cancer* 112(3):458-464.

Mofenson, H.C. *et al*. 1981. Baby powder--a hazard! *Pediatrics* 68(2):265-266.

Moller, P. *et al.* 2010. Role of oxidative damage in toxicity of particulates. *Free Radic. Res.* 44(1):1-46.

Moller, P. *et al.* 2013. Oxidatively damaged DNA in animals exposed to particles. *Crit. Rev. Toxicol* 43(2):96-118.

Molnar, J.J., G. Nathenson, and S. Edberg. 1962. Fatal aspiration of talcum powder by a child: report of a case. *N. Engl. J. Med.* 266:36-37.

Moon, M.C. *et al.* 2011. Risk assessment of baby powder exposure through inhalation. *Toxicol. Res.* 27(3):137-141.

Moss, M.H. 1969. Dangers from talcum powder. *Pediatrics* 43(6):1058

Muscat, J. and M. Huncharek. 2005. Talc and anti-MUC1 antibodies. *Cancer Epidemiol. Biomarkers Prev.* 14(11 Pt 1):2679.

Muscat, J.E. and M.S. Huncharek. 2008. Perineal talc use and ovarian cancer: a critical review. *Eur. J. Cancer Prev.* 17(2):139-146.

Nam, K. and D.R. Gracey. 1972. Pulmonary talcosis from cosmetic talcum powder. *JAMA* 221(5):492-493.

National Institute for Occupational Health and Safety (NIOSH). 1980. *Workplace Exposure to Asbestos: Review and Recommendations*. U.S. Department of Health and Human Services. [https://www.cdc.gov/niosh/docs/81-103/pdfs/81-103.pdf?id=10.26616/NIOSHPUB81103]

National Research Council (NRC). 1983. *Risk assessment in the Federal Government: Managing the process.* National Academy Press: Washington, DC.

National Research Council (NRC). 2011. *Reference Manual on Scientific Evidence.* 3rd edition, The National Academies Press: Washington, D.C.

National Toxicology Program (NTP). 1998. Report on Carcinogens Background Document for Silica, Crystalline (Respirable Size). December 2 - 3, 1998. *[https://ntp.niehs.nih.gov/ntp/newhomeroc/other_background/silica_no_app_508.pdf]*

National Toxicology Program (NTP). 1993. NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6) (Non-Asbestiform) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). *Natl. Toxicol. Program Tech. Rep. Ser.* 421:1-287.

National Toxicology Program (NTP). 2016. *NTP Report on Carcinogens, Fourteenth Edition. Asbestos (CAS No. 1332-21-4)*. National Toxicology Program, Department of Health and Human Services.

Natow, A.J. 1986. Talc: need we beware? *Cutis* 37(5):328-329.

Ness, R.B. and C. Cottreau. 1999. Possible role of ovarian epithelial inflammation in ovarian cancer. *J. Natl. Cancer Inst.* 91(17):1459-1467.

Ness, R.B. *et al.* 2000. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 11(2):111-117.

Newhouse, M.L. *et al.* 1972. A study of the mortality of female asbestos workers. *Br. J. Ind. Med.* 29(2):134-141.

Newhouse, M.L., G. Berry, and J.C. Wagner. 1985. Mortality of factory workers in east London 1933-80. *Br. J. Ind. Med.* 42(1):4-11.

O'Brien, K.M. *et al.* 2020. Association of powder use in the genital area with risk of ovarian cancer. JAMA 323(1):49-59.

O'Brien, K.M. *et al.* 2024. Intimate care products and incidence of hormone-related cancers: a quantitative bias analysis. *J. Clin. Oncol.* 00:1-15.

Oliver, T. 1927. Clinical Aspects of Pulmonary Asbestosis. *Br. Med. J.* 2(3491):1026-1027.

Paoletti, L. *et al.* 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. *Regul. Toxicol. Pharmacol.* 4(3):222-235.

Parmley, T.H. and J.D. Woodruff. 1974. The ovarian mesothelioma. *Am. J. Obstet. Gynecol.* 120(2):234-241.

Pelling, D. and J.G. Evans. 1986. Long-term peritoneal tissue response in rats to mould-release agents and lubricant powder used on surgeons' gloves. *Food Chem. Toxicol* 24(5):425-430.

Penninkilampi, R. and G.D. Eslick. 2018. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology* 29(1):41-49.

Phillips, J.C. *et al.* 1978. Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. *Food Cosmet. Toxicol* 16(2):161-163.

Phung, M.T. *et al.* 2022. Effects of risk factors for ovarian cancer in women with and without endometriosis. *Fertil. Steril.* 118(5):960-969.

Pooley, F.D. and N. Rowlands. 1975. Chemical and physical properties of British talc powders. *Inhaled. Part* 4(2):639-646.

Porro, F.W., J.R. Patton, and A.A. Hobbs Jr. 1942. Pneumoconiosis in the talc industry. *Am. J. Roentgenol.* 47(4):507-524.

Porro, F.W. and N.M. Levine. 1946. Pathology of talc pneumoconiosis with report of an autopsy. *North. NY Med. J.* 3:23-25.

Pott, F. and K.H. Friedrichs. 1972. [Tumors in the rat following intraperitoneal injections of fibrous dust]. *Naturwissenschaften* 59(7):318

Pott, F., F. Huth, and K.H. Friedrichs. 1974. Tumorigenic effect of fibrous dusts in experimental animals. *Environ. Health Perspect.* 9:313-315.

Purdie, D. *et al.* 1995. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study: survey of Women's Health Study group. *Int. J. Cancer* 62(6):678-684.

Radic, I. *et al.* 1988. Immunosuppression induced by talc granulomatosis in the rat. *Clin. Exp. Immunol.* 73(2):316-321.

Rakoff-Nahoum, S. 2006. Why cancer and inflammation? *Yale J. Biol. Med.* 79(3-4):123-130.

Rehman, G. *et al.* 2013. Determination of toxic heavy metals in different brands of talcum powder. *Int. J. Appl. Nat. Sci.* 2(2):45-52.

Roberts, G.B. 1947. Granuloma of the fallopian tube due to surgical glove talc; silicious granuloma. *Br. J. Surg.* 34(136):417-423.

Rohl, A.N. and A.M. Langer. 1974. Identification and quantitation of asbestos in talc. *Environ. Health Perspect.* 9:95-109.

Rohl, A.N. *et al.* 1976. Consumer talcums and powders: mineral and chemical characterization. *J. Toxicol. Environ. Health* 2(2):255-284.

Rosenblatt, K.A., M. Szklo, and N.B. Rosenshein. 1992. Mineral fiber exposure and the development of ovarian cancer. *Gynecol. Oncol.* 45(1):20-25.

Rosenblatt, K.A. *et al.* 2011. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control* 22(5):737-742.

Rothman, K.J. and S. Greenland. 1998. Causation and causal inference. In: *Modern Epidemiology*, *2nd Edition*. K.J. Rothman and S. Greenland (eds.), Lippincott Williams & Wilkins: Philadelphia, chapter 2.

Rubino, G.F. *et al.* 1976. Mortality study of talc miners and millers. *J. Occup. Med.* 18(3):187-193.

Saed, G.M., M.P. Diamond, and N.M. Fletcher. 2017. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecol. Oncol.* 145(3):595-602.

Saed, G.M., R.T. Morris and N.M. Fletcher (March 28, 2018). New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress, Ovarian Cancer, Omer Devaja and Andreas Papadopoulos, IntechOpen, DOI: 10.5772/intechopen.73860. [https://www.intechopen.com/books/ovarian-cancer-from-pathogenesis-to-treatment/new-insights-into-the-pathogenesis-of-ovarian-cancer-oxidative-stress]

Savant, S.S. *et al.* 2018. The role of inflammation and inflammatory mediators in the development, progression, metastasis, and chemoresistance of epithelial ovarian cancer. *Cancers* 10:251.

Sax, N.I. 1957. *Dangerous Properties of Industrial Materials. A completely revised and enlarged edition of Handbook of Dangerous Materials.* Reinhold Publishing Corporation: New York.

Saxen, A. and P.I. Tuovinen. 1947. Experimental and clinical observations on granulomas caused by talc and some other substances. *Acta Chir. Scand.* 96(2):131-151.

Schepers, G.W. and T.M. Durkan. 1955. The effects of inhaled talc-mining dust on the human lung. *AMA Arch. Ind. Health* 12(2):182-197.

Schildkraut, J.M. *et al.* 2016. Association between body powder use and ovarian cancer: the African American cancer epidemiology study (AACES). *Cancer Epidemiol. Biomarkers Prev.* 25(10):1411-1417.

Schulz, R.Z. and C.R. Williiams. 1942. Commercial talc: animal and mineralogical studies. *J. Ind. Hyg. Toxicol.* 24(4):75-79.

Seeler, A., J.S. Gryboski, and H.E. MacMahon. 1959. Talc pneumoconiosis. *AMA Arch. Ind. Health* 19(4):392-402.

Seiler, H.E. 1928. A case of pneumoconiosis: Result of the inhalation of asbestos dust. *Br. Med. J.* 2(3543):982-980.

Selikoff, I.J., J. Churg, and E.C. Hammond. 1964. Asbestos exposure and neoplasia. *JAMA* 188:22-26.

Senthil, K., S. Aranganathan, and N. Nalini. 2004. Evidence of oxidative stress in the circulation of ovarian cancer patients. *Clin. Chim. Acta* 339(1-2):27-32.

Shim, I. *et al.* 2015. Inhalation of talc induces infiltration of macrophages and upregulation of manganese superoxide dismutase in rats. *Int. J. Toxicol.* 34(6):491-499.

Shukla, A. *et al.* 2009. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *Am. J. Respir. Cell. Mol. Biol.* 41(1):114-123.

Shushan, A. *et al.* 1996. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil. Steril.* 65(1):13-18.

Sjosten, A.C., H. Ellis, and G.A. Edelstam. 2004. Retrograde migration of glove powder in the human female genital tract. *Hum. Reprod.* 19(4):991-995.

Stanton, M.F. *et al.* 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. *J. Natl. Cancer Inst.* 67(5):965-975.

Stenback, F. and J. Rowlands. 1978. Role of talc and benzo(a)pyrene in respiratory tumor formation. An experimental study. *Scand. J. Respir. Dis.* 59(3):130-140.

Stenback, F., V-M. Wasenius and J. Rowland. 1986. Alveolar and interstitial changes in silicate-associated lung tumors in Syrian hamsters. In: *Silica, Silicosis, and Cancer:Controversy in Occupational Medicine*, *Vol. 2 edition*, chapter 21.

Stuart, B.O. 1984. Deposition and clearance of inhaled particles. *Environ. Health Perspect.* 55:369-390.

Suzuki, Y. and N. Kohyama. 1991. Translocation of inhaled asbestos fibers from the lung to other tissues. *Am. J. Ind. Med.* 19(6):701-704.

Taher, M.K. *et al.* 2020. Critical review of the association between perineal use of talc powder and the risk of ovarian cancer. *Reprod. Toxicol.* 90:88-101.

Tarchi, M. *et al.* 1994. Cohort mortality study of rock salt workers in Italy. *Am. J. Ind. Med.* 25(2):251-256.

Terry, K.L. *et al.* 2013. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev. Res. (Phila)* 6(8):811-821.

Trabert, B. *et al.* 2014. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. *Gynecol. Oncol.* 135(2):297-304.

Trautwein, G. and C.F. Helmboldt. 1967. Experimental pulmonary talcum granuloma and epithelial hyperplasia in the chinchilla. *Pathol. Vet.* 4(3):254-267.

Tye, M.J., K. Hashimoto, and F. Fox. 1966. Talc granulomas of the skin. *JAMA* 198(13):1370-1372.

Tzonou, A. *et al.* 1993. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int. J. Cancer* 55(3):408-410.

United States Geological Survey (USGS). 2001. *Some Facts About Asbestos.* U.S. Department of the Interior. *[https://www.luc.edu/media/lucedu/environmentalservices/images/facilities/asbestos_fact_sheet_usgs.pdf]*

van Huisstede, A. *et al.* 2010. Talcosis due to abundant use of cosmetic talcum powder. *Eur. Respir. Rev.* 19(116):165-168.

Venter, P. F. and M. Iturralde. 1979. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S. Afr. Med. J.* 55(23):917-919.

Wagner, J.C. *et al.* 1975. Animal experiments with talc. *Inhaled. Part* 4(2):647-654.

Wang, X. *et al.* 2013. Cause-specific mortality in a Chinese chrysotile textile worker cohort. *Cancer Sci.* 104(2):245-249.

Wehner, A.P. *et al.* 1985. Do particles translocate from the vagina to the oviducts and beyond? *Food Chem. Toxicol.* 23(3):367-372.

Wehner, A.P., R.E. Weller, and E.A. Lepel. 1986. On talc translocation from the vagina to the oviducts and beyond. *Food Chem. Toxicol.* 24(4):329-338.

Wells, I.P., P.A. Dubbins, and W.F. Whimster. 1979. Pulmonary disease caused by the inhalation of cosmetic talcum powder. *Br. J. Radiol.* 52(619):586-588.

Whittemore, A.S. *et al.* 1988. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am. J. Epidemiol.* 128(6):1228-1240.

Whysner, J. and M. Mohan. 2000. Perineal application of talc and cornstarch powders: evaluation of ovarian cancer risk. *Am. J. Obstet. Gynecol.* 182(3):720-724.

Wignall, B.K. and A.J. Fox. 1982. Mortality of female gas mask assemblers. *Br. J. Ind. Med.* 39(1):34-38.

Wong, C. *et al.* 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet. Gynecol.* 93(3):372-376.

Wood, W.B. 1929. Pulmonary asbestosis. *Tubercle* 23:353-363.

Woolen, S.A. *et al.* 2022. Association between the frequent use of perineal talcum powder products and ovarian cancer: a systematic review and meta-analysis. *J. Gen. Intern. Med.* 37(10):2526-2532.

World Health Organization (WHO). 2000. *Crystalline Silica, Quartz.* World Health Organization. *[https://www.who.int/ipcs/publications/cicad/en/cicad24.pdf]*

World Health Organization (WHO). 2011. Update of the scientific evidence on asbestos and cancer. [*http://www.who.int/phe/news/events/international_conference/Session2_DrStraif.pdf*]

Wright, H.R. *et al.* 1996. Potential toxicity of retrograde uterine passage of particulate matter. *J. Long Term Eff. Med. Implants* 6(3-4):199-206.

Wu, A.H. *et al.* 2009. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int. J. Cancer* 124(6):1409-1415.

Wu, A.H. *et al.* 2015. African Americans and Hispanics remain at lower risk of ovarian cancer then Non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. *Cancer Epidemiol. Biomark. Prevent.* 24:1094-1100.

Zazenski, R. *et al.* 1995. Talc: occurrence, characterization, and consumer applications. *Regul. Toxicol. Pharmacol.* 21(2):218-229.

Zervomanolakis, I. *et al.* 2007. Physiology of upward transport in the human female genital tract. *Ann. NY Acad. Sci.* 1101:1-20.

APPENDIX A

Curriculum Vita

CURRICULUM VITAE

Laura M. Plunkett, Ph.D., D.A.B.T

ADDRESS 1127 Eldridge Pkwy, Suite 300335
Houston, TX 77077

EDUCATION

1984	Ph.D.	Pharmacology	University of Georgia
1980	B.S.	Zoology	University of Georgia

PROFESSIONAL EXPERIENCE

Registered Patent Agent Licata & Tyrrell, P.C., Marlton, N.J., 1999 – present
Assists clients with obtaining patent protection, specializing in products used in medical applications (drugs, devices, dietary supplements). Assists clients with developing regulatory strategies for commercialization of their inventions. Provides regulatory support for companies engaged in manufacturing and marketing of products regulated by the U.S. Food and Drug Administration, the U.S. Environmental Protection Agency and other regulatory bodies in the U.S. and worldwide.

Partner. BioPolicy Solutions LLC, June 2020 – present
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

President. Integrative Biostrategies (IB) LLC, 2001- May 2020
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provides litigation support services as both consulting expert and testifying expert.

Owner. Plunkett & Associates, Houston, Texas, 1997 – 2001
Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and

Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Houston, Texas, 1992 – 1997

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug Administration. Provided litigation support services as both consulting expert and testifying expert.

Manager. ENVIRON Corporation, Arlington, Virginia, 1989 – 1992

Consultant to a variety of clients in areas of pharmacology, toxicology, risk assessment and regulatory strategy. Focus on products regulated by the U.S. Food and Drug administration.

Assistant Professor. University of Arkansas for Medical Sciences, Department of Pharmacology and Toxicology, 1986 – 1989

Taught medical and graduate student courses in pharmacology (lecture and laboratory), neurosciences, cardiovascular pharmacology, and neuropharmacology. Performed basic research in area of autonomic control of cardiovascular function and neurochemical systems involved in autonomic function. Recipient of extramural funding from the Arkansas Heart Association (principal investigator).

Postdoctoral fellow. National Institute of General Medical Sciences, Pharmacology Research Associate Training Program, 1984 – 1986

Performed basic research in area of neurochemical control of cardiovascular function and neurochemical systems involved in autonomic function.

Research Assistant. University of Georgia, College of Pharmacy, Department of Pharmacology and Toxicology 1980 – 1984

Taught laboratory courses in pharmacology to pharmacy students as part of graduate student assistantship responsibilities.

HONORS AND AWARDS

Chosen for PRAT program at National Institutes of Health. Pharmacology Research Associate Training Program, 1984-1986.

Rho Chi. The University of Georgia, College of Pharmacy, Initiated, 1984.

Recipient of Excellence in Graduate Research Award. The University of Georgia, College of Pharmacy, 1983.

Alpha Lambda Delta. The University of Georgia Chapter, 1978.

PROFESSIONAL CERTIFICATION

Registered patent agent, 1999 [Registration No. 45,015]
Diplomate, American Board of Toxicology, 1993 to present.

ACADEMIC AFFILIATION

Adjunct Professor. Baylor University, Department of Environmental Science, 2017-present

PROFESSIONAL MEMBERSHIPS

Member, Society of Toxicology 1992 – present

President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2021-2022

Vice-President, Society of Toxicology Risk Assessment Specialty Section (RASS) 2020-2021

Vice-President Elect, Society of Toxicology Risk Assessment Specialty Section (RASS) 2019-2020

Member, Lone Star Chapter Society of Toxicology 2007 – present

Councilor, Lone Star Chapter Society of Toxicology 2010 - 2013

Secretary, Lone Star Chapter Society of Toxicology 2013 – 2015

Vice President, Lone Star Chapter Society of Toxicology 2015-2016

President, Lone Star Chapter, Society of Toxicology 2016-2017

Past President, Lone Star Chapter, Society of Toxicology 2017-2018

Member, American College of Toxicology, 1997 - present

Member, Society for Risk Analysis, 2007- present

President, Lone Star Chapter of the Society for Risk Analysis, 1998

Councilor, Lone Star Chapter of the Society for Risk Analysis, 1999-2000

Member, Regulatory Affairs Professionals Society, 2003 - present

Member, Society for Neuroscience 1985 - present

Member, American Association for Pharmaceutical Sciences 1992 – present

Member, Society for Environmental Geochemistry and Health 1992 - present

Member, ASTM Committee E06, 1990 – present

Member, International Association of Plumbing and Mechanical Officials (IAPMO) Committee Z1123 (Prop 65) Committee, 2020 - present

PUBLICATIONS

1. Bobst, S, Ryan, K, **Plunkett, LM,** Willett, KL. 2020. ToxPoint: Toxicology studies on Δ9-tetrahydrocannabinol and cannabidiol-containing products available to consumers are lacking. *Toxicol. Sci.* 178:1-2.

2. Rajendran, N, Seagrave, JC, **Plunkett, LM**, MacGregor, JA. A comparative assessment of the acute inhalation toxicity of vanadium compounds. *Inhal. Toxicol.* 2016. 28:618-628.

3. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well can in vitro data predict in vivo effects of chemicals? Rodent carcinogenicity as a case study. *Regul. Toxicol. Pharmacol.* 2016. 77:54-64.

4. **Plunkett, LM**, Kaplan, AM, Becker, RA. Challenges in using the ToxRefDB as a resource for toxicity modeling. *Regul. Toxicol Pharmacol*. 2015. 72:610-614.

5. **Plunkett, LM**, Becker, RA, Kaplan, M. An enhanced tiered toxicity testing framework with triggers for assessing hazards and risks of commodity chemicals. *Regul. Toxicol. Pharmacol*. 2010. 58:382-394.

6. Chambers, A, Krewski, D, Birkett, N, **Plunkett, L,** Hertzberg, R, Danzeisen, R, Aggett, PJ, Starr, TB , Baker, S, Dourson, M, Jones, P, Keen, CL , Meek, B, Schoeny, R, and Slob, W *J.* An exposure-response curve for copper excess and deficiency.

Toxicol. Environ. Health. 2010. 13:546- 578.

7. Krewski, D, Chambers, A, Stern, BA, Aggett, PA, **Plunkett, L,** Rudenko, L. Development of a copper database for exposure-response analysis. *J. Toxicol. Environ. Health.* 2010. 73:208-216.

8. **Plunkett, LM**, Becker, RA. Does the standard toxicological testing paradigm for industrial chemicals apply to screening for children's health risks? *The Open Toxicol. J.* 2008, 2:42-60.

9. Becker, RA, **Plunkett, LM**, Borzelleca, JF, Kaplan, AM. Tiered toxicity testing: Evaluation of toxicity-based decision triggers for human health hazard characterization. *Food Chem. Toxicol*. 2007, 45:2454-2469.

10. MacGregor, JA, **Plunkett, LM**, Youngren, SH, Manley, A, Plunkett, JB, Starr, TB. Humans Appear No More Sensitive than Laboratory Animals to the Inhibition of Red Blood Cell Cholinesterase by Dichlorvos (DDVP). *Regul. Toxicol. Pharmacol*., 2005, 43:150-167.

11. **Plunkett, LM.** Do current FIFRA guideline tests protect infants and children? Lead as a case study. *J Regul Toxicol Pharmacol* 1999;29:80-87.

12. **Plunkett, LM,** Seifen E, Kennedy RH. Effect of morphine pretreatment on cocaine cardiotoxicity in anesthetized guinea pigs. *Arch Int Pharmacodyn* 1989;297:60-67.

13. Zorbas M., Owens SM, **Plunkett LM,** Bui H. The pharmacokinetics of [3H]-[1-(2-thienyl)cyclohexyl]piperidine (TCP) in Sprague Dawley rats. *J Drug Metab Disposit* 1989;17:641-645.

14. Seifen E, **Plunkett LM,** Kennedy RH. Cardiovascular and lethal effects of cocaine in anesthetized dogs and guinea pigs. *Arch Int Pharmacodyn* 1989;300:241-253.

15. McCarty R, **Plunkett LM.** Regulation of binding sites for atrial natriuretic factor (ANF) in rat brain. *Peptides* 1988;9(S1):3-8.

16. Stewart RE, Swithers SE, **Plunkett LM,** McCarty R. ANF receptors: distribution and regulation in central and peripheral tissues. *Neurosci Biobehav Rev* 1988;12:151-168.

17. **Plunkett LM,** Tackett RL. Central dopamine receptors and their role in digoxin-induced cardiotoxicity in the dog. *J Pharm Pharmacol* 1987;39:29-34.

18. **Plunkett LM,** Tackett RL. Increases in CSF norepinephrine associated with the

onset of cardiac glycoside toxicity. *Eur J Pharmacol* 1987;136:119-122.

19. McCarty R, **Plunkett LM.** Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. *Brain Res Bull* 1987;18:289-94.

20. **Plunkett LM,** Shigematsu K, Kurihara M, Saavedra JM. Localization of angiotensin II receptors along the anteroventral-third ventricle area of the rat brain. *Brain Res* 1987;405:205-212.

21. Israel A, **Plunkett LM,** Saavedra JM. Increased number of angiotensin II binding sites determined by autoradiography in anterior pituitary of water deprived and Brattleboro rats. *Neuroendocrinol* 1986;42:57-63.

22. Saavedra JM, Correa FMA, **Plunkett LM,** Israel A, Kurihara M, Shigematsu K. Angiotensin and atrial natriuretic peptide binding in brain of hypertensive rats. *Nature* 1986;320:758-760.

23. McCarty RM, **Plunkett LM.** Forebrain atriopeptin binding sites: Alterations in spontaneously hypertensive rats. *Neurochem Int* 1986;9:177-183.

24. Shigematsu K, Saavedra JM, **Plunkett LM,** Kurihara M, Correa FMA. Angiotensin II binding sites in the anteroventral-third-ventricle (AV3V) area and related structures of the rat brain. *Neurosci Lett* 1986 67:37-41.

25. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative distribution of angiotensin-converting enzyme (kininase II) in discrete areas of the rat brain by autoradiography with computerized microdensitometry. *Brain Res* 1986;275:259-266.

26. Saavedra JM, Israel A, **Plunkett LM,** Kurihara M, Shigematsu K, Correa FMA. Quantitative distribution of angiotensin II binding sites in rat brain by autoradiography. Peptides 1986;7:679-687.

27. McCarty R, **Plunkett LM**. Binding sites for atrial natriuretic factor (ANF) in brain: alterations in Brattleboro rats. *Brain Res Bull* 1986;17:767-772.

28. **Plunkett LM,** Gokhale RD, Vallner JJ, Tackett RL. Prazosin alters free and total plasma digoxin in dogs. *Am Heart J* 1985;109:847-851.

29. **Plunkett LM,** Tackett RL. The effects of central beta-receptor antagonism on digoxin cardiotoxicity. *Res Comm Chem Path Pharmacol* 1985;48:209-220.

30. Israel A, Saavedra JM, **Plunkett L.** Water deprivation upregulates angiotensin II

receptors in rat anterior pituitary. *Am J Physiol* 1985;248 (Endocrino. Metabl. II):E264-E267.

31. Niwa M, Shigematsu K**, Plunkett L,** Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. *Am J Physiol* 1985;249 (Heart Circ. Physiol 18):H694-H697.

32. Correa FMA, **Plunkett LM,** Saavedra JM, Hichens M. Quantitative autoradiographic determination of angiotensin-converting enzyme (kininase II) kinetics in individual rat brain nuclei with 125I-351A, a specific enzyme inhibitor. *Brain Res* 1985;347:192-195.

33. Israel A, Niwa M, **Plunkett LM,** Saavedra JM. High affinity angiotensin receptors in rat adrenal medulla*.* *Regul Pept* 1985;11:237-243.

34. Israel A, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic characterization of receptors for angiotensin II and other neuropeptides in individual brain nuclei and peripheral tissues from single rats. *Cell Mol Neurobiol* 1985;5:211-222.

35. **Plunkett LM,** Correa FMA, Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme kinetics in rat pituitary and adrenal glands with 125I-135A, a specific inhibitor. Regul Pept 1985;12:1-10.

36. **Plunkett LM,** Saavedra JM. Increased angiotensin II binding affinity in the nucleus tractus solitarius of spontaneously hypertensive rats. *Proc Natl Acad Sci* 1985;82:7721-7724.

37. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digoxin cardiotoxicity. *J Pharmacol Exp Ther* 1983;227:683-686.

ABSTRACTS

1. Woodall, G.M., Grimm, F.A, Pechacek, N., Wignall, J., Minsavage, G.D. and **Plunkett, L.M.** Risk Assessment Syllabus. Society of Toxicology annual meeting, March 19-23, 2023, Nashville, TN.

2. **Plunkett, L.M.** Cannabidiol Incorporation into Consumer Products in the US: Regulatory Challenges to Commercialization. Presenting at the Society of Toxicology annual meeting. March 25, 2021. Virtual Meeting.

3. **Plunkett, LM**. Cannabidiol Incorporation into Consumer Products in the US:

Regulatory Challenges to Commercialization. Presenting at the annual meeting of the American Association for the Advancement of Science (AAAS), February 8-11, 2021. Virtual meeting

4. **Plunkett, LM**. Marijuana and Public Safety Concerns: States in Charge. Presenting at Society of Toxicology annual meeting. March 11-15, 2018, San Antonio, Texas.

5. Cox, LA, Popken, DA, Kaplan, AM, **Plunkett, LM**, Becker, RA. How well do High Throughput Screening (HTS) assay data predict in vivo rodent carcinogenicity of pesticides? Presenting at Society for Risk Analysis annual meeting, December 11-15, 2016, San Diego, California.

6. **Plunkett, LM**. THC and legal issues related to the state of the science. Symposium presenter at the Society of Toxicology, New Orleans, LA, March 2016.

7. Goyak, K, Alyea, R, Becker, RA, **Plunkett, LM**, Plunkett, JB. Evaluating the ability of high-throughput screening (HTS) assays to capture the biological activity of industrial chemicals. Poster presentation at the Society of Toxicology, New Orleans, LA, March 2016.

8. MacGregor, JA, Plunkett, JB, **Plunkett, LM.** The occurrence of chemically induced lung tumors in rodents as an outcome in NTP chronic bioassays and the impact on cancer classifications. Presented at the Society of Toxicology, San Diego, CA, March 2015.

9. Urban, JD, Thompson, CM, **Plunkett, LM**, Perry, C, Haws, LC. A state of the science of copper reference dose for soil remediation. Presented at the Society of Toxicology, San Diego, CA, March 2015.

10. **Plunkett, LM**, Kaplan, AM, Becker, RA. Evaluation of a tiered toxicity testing decision trigger for assessing reproductive hazards of commodity chemicals. Submitted for presentation at the Society of Toxicology, Phoenix, AZ, March 2014.

11. **Plunkett, L.M.** Overview of key public and worker health concerns in Texas food production. Presented at the Society of Toxicology, San Antonio, TX, March 2012.

12. **Plunkett, L.M.**, Starr, T.B., MacGregor, J.A., Manley, A. Corn oil as a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice exposed by gavage. Presented at Society of Toxicology, Washington, D.C., March 9, 2011. [Award received for "Best Presentation"]

13. **Plunkett, LM**, MacGregor, JA, Starr, TB, Manley, A. Daily gavage with corn oil is a causative factor for proliferative lesions of the forestaomach in B6C3F1 mice.

Toxicology Lett. 189S:S142. Presented at EUROTOX, Dresden, Germany, September 14, 2009.

14. **Plunkett, LM**, MacGregor, JA, Starr, TB, Youngren, SH, Manley, A. Determination of a dichlorvos-specific acute interspecies uncertainty factor. Society of Toxicology, Seattle, WA, March 19, 2008.

15. **Plunkett, LM**, Starr, TB, Youngren, SH, MacGregor, JA, Manley, A. Determination of the magnitude of intraspecies differences in red blood cell cholinesterase inhibition in response to dichlorvos exposure. Society of Toxicology, San Diego, CA, March 6, 2006.

16. **Plunkett, LM**, Licata, JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Orlando, FL, March 4, 2006.

17. **Plunkett, LM,** Licata JM. What every technology manager needs to know about FDA law. Association of University Technology Managers (AUTM), Phoenix, AZ February 2005.

18. **Plunkett, LM**. Qualitative Interpretation of Complex and Disparate Data Sets for Dose-Response Assessment of Essential Trace Elements: Copper as a Case Study. Society for Toxicology, Baltimore, MD March 2004 .

19. **Plunkett, LM.** Evaluating qualitative and quantitative dose-response data in complete data sets for comparative dose-response assessment. Soc. Risk Analysis, Baltimore, MD, December 10, 2003.

20. **Plunkett, LM**, Rieth S, Starr T. Issues in assessing risks for cholinesterase-inhibiting pesticides: A decision tree approach. Soc. Risk Analysis, New Orleans, LA, December 9-12, 1996

21. **Plunkett, LM**, Brown S. Assessment of the potential neuropathic risk to banana workers from dermal exposure to chlorpyrifos. Soc. Risk Analysis, Honolulu, HI, December 3-7, 1995

22. **Plunkett, LM**, Russell K. Cooperation versus Confrontation: Reconciling Lead regulations, exposure studies, and public perception. SEGH Conference, July, Salt Lake City, UT, 1994

23. **Plunkett LM**, Wixtrom RN, Cabrera CR. Evaluation of the long-term safety of inflatable penile prostheses: a critical analysis of potential carcinogenic, reproductive, teratogenic, or adverse immunological effects of silicone. Western Section of American Urological Association Meeting, Seattle, WA, August 21-25, 1994

24. Wixtrom RN, **Plunkett LM**, Clarkin CM. Complications of inflatable penile prostheses: A comprehensive review of infection, mechanical complications, erosion/migration/extrusion, and fibrous capsule formation. 1994.

25. Wixtrom RN, Clarkin CM, Purkait B, **Plunkett LM**. A review of clinical experience with the Mentor Alpha I and Mark II inflatable penile prostheses. 1994.

26. **Plunkett LM**, Rosolowsky LJ, Lerner DM, Washburn ST. A biokinetic model for predicting blood lead levels in adults living near a former battery recycling facility. SEGH Conference, New Orleans, LA, July, 1993.

27. Rosolowsky LJ, Edelmann KG, **Plunkett LM**. A biokinetic model for predicting blood lead levels in adults that accounts for intermittent exposures. Society for Risk Analysis, December, 1993

28. **Plunkett LM**, Owens SM , Gunnell M, Owens RB. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) dosing on [3H]TCP and [3H] haloperidol binding in rat brain. *FASEB J* 1990;4:A329.

29. Owens RB, Owens SM, Gunnell M, **Plunkett LM**. 1990. The effect of chronic phencyclidine (PCP) and phenylcyclohexene (PC) on lymphocyte in subsets in rats. *FASEB J* 1990;4:A337.

30. Zorbas M, Owens SM, **Plunkett LM**, Bui H. [3H]TCP protein binding and pharmacokinetics in Sprague-Dawley rat. *FASEB J* 1989;3:A1036.

31. **Plunkett LM**, Kennedy RH, Seifen E. Effects of chronic stress on myocardial beta-adrenergic receptor binding. *The Pharmacologist* 1988;A1300.

32. Evans, R.E., **Plunkett LM**, Kennedy RH, Seifen E. [3H]Ouabain binding to regions of rat heart as determined by autoradiography. *The Pharmacologist* 1988;A41.

33. Massey BW, **Plunkett LM**, Kennedy RH, Seifen E. Alterations in brain angiotensin II binding in the aged rat. Soc. Neuroscience 1987 Abstracts, p. 722.

34. **Plunkett LM**, Alexander N, Saavedra JM. Altered angiotensin II binding in adrenal gland, pituitary gland and brain of sinoaortic denervated rats. Am. Soc. Hypertension. New York, NY, May 1986.

35. Saavedra JM, **Plunkett LM**, Correa FMA. Increased number of angiotensin II binding sites in the subfornical organ of spontaneously hypertensive rates. Am. Soc. Hypertension, New York, NY, May 1986.

36. **Plunkett LM**, Niwa M, Shigematsu K, Saavedra JM. Increased angiotensin II (ANG) binding in superior cervical ganglia of spontaneously hypertensive rats (SHR). *Fed. Proc* 1985;3: 498.

37. **Plunkett LM**, Saavedra JM. Discrete localization of angiotensin II (ANG) binding sites in rat brainstem by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, D.C., May, 1985.

38. **Plunkett LM**, Israel A, Niwa M, Shigematsu K, Saavedra JM. Alterations in angiotensin II binding in pituitary gland, adrenal gland and superior cervical ganglia of spontaneously hypertensive rats (SHR) as determined by quantitative autoradiography. Neural and Endocrine Peptides and Receptors, Symposium, Washington, DC, May 1985.

39. Shigematsu K, Niwa M, **Plunkett LM**, Saavedra JM. High affinity substance P binding sites in rat sympathetic ganglia. Neural and Endocrine Peptide and Receptors, Symposium '85, Washington, DC, May 1985.

40. McCarty R, **Plunkett LM**, Israel A, Saavedra JM. Quantitation of somatostatin binding sites in rat brain. Neural and Endocrine Peptides and Receptors, Symposium '85, Washington, DC, May, 1985.

41. **Plunkett LM**, Saavedra JM. Increased angiotensin II (ANG) binding in brainstem nuclei of adult spontaneously hypertensive rats (SHR) by quantitative autoradiography. Interamerican Society of Hypertension, Cleveland, OH, May 1985.

42. Saavedra JM, **Plunkett LM**, Niwa M, Israel A, Shigematsu K, R. McCarty, Correa FMA. Autoradiographic-microdensitometric methods for the kinetic analysis of neuropeptide receptors and peptidases in individual brain nuclei. IVth World Congress of Biological Psychiatry, Philadelphia, PA, September, 1985.

43. **Plunkett LM** Saavedra JM. 1985. Altered angiotensin II binding in ganglia and brainstem nuclei of spontaneously hypertensive rats (SHR). Council for High Blood Pressure Research, Cleveland, OH, September 1985.

44. **Plunkett LM**, Correa FMA, Saavedra JM. Quantification of angiotensin-1-converting enzyme kinetics in individual rat pituitary and adrenal glands with 125I-MK351A, a specific enzyme inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

45. McCarty R**, Plunkett LM**, Shigematsu K, Saavedra JM. Quantitative autoradiographic analysis of somatostatin binding sites in discrete areas of rat brain. Society for Neuroscience, Dallas, Texas, October, 1985.

46. Correa FMA, **Plunkett LM,** Saavedra JM. Quantitative autoradiographic determination of angiotensin-converting enzyme distribution in rat brain with 125I-MK351A, a specific inhibitor. Society for Neuroscience, Dallas, Texas, October 1985.

47. **Plunkett LM,** Saavedra JM. Altered angiotensin II binding kinetics in brainstem, pituitary gland, and adrenal gland in adult SHR. 5th International Symposium on SHR and Related Studies, Tokyo, Japan, October, 1985.

48. **Plunkett LM,** Tackett RL. CSF catecholamine activity decreases during cardiac glycoside-induced arrhythmogenesis. *The Pharmacologist* 1985; 25:745.

49. Tackett RL**, Plunkett LM**. Naloxone inhibits the central hypotensive actions of propranolol. *The Pharmacologist* 1983;25:101.

50. **Plunkett LM,** Vallner JJ, Tackett RL. Prazosin lowers plasma digoxin levels. American Heart Assoc, pp 15, Savannah, GA, 1983.

51. Tackett RL**, Plunkett LM**. 1983. BHT 933 lowers blood pressure and increases cerebrospinal fluid norepinephrine levels. American Heart Assoc, pp 16, Savannah GA, 1983.

52. Bayoumi SM, Gokhale R, **Plunkett L,** Vallner JJ. Pharmacokinetics of clortrimazole in dogs. *Acad. Pharmaceut. Sci* 1983;13(2):204, (Miami meeting).

53. **Plunkett LM,** Tackett RL. Central alpha receptors and their role in digitalis cardiotoxicity. *The Pharmacologist* 1982; 24:489A.

54. **Plunkett LM,** Tackett RL. Central alpha antagonism decreases blood pressure in the dog. Proc. Soc. Exp. Biol. Med. S.E. Sec. 7:12A 1982.

PRESENTATIONS

1. **Plunkett, LM.** Reproductive Toxicology. Invited lecture at NYU, Department of Environmental Medicine. October 28, 2020.

2. **Plunkett, L.M.** Provided public comments at the FDA-sponsored public meeting on "Testing Methods for Asbestos in Talc and Cosmetic Products Containing Talc", February 4, 2020.

3. **Plunkett, L.M.** Pesticide Toxicology. Invited lecture at NYU, Department of Environmental Medicine. December 4, 2019.

4. **Plunkett, L.M.** Practical applications of risk assessment. Lecturer at University of Texas Medical Branch at Galveston, Department of Pharmacology and Toxicology. October 19, 2018.

5. **Plunkett, LM.** Non-obviousness and §103. Lecturer at Rutgers School of Law, Camden Campus. November 6, 2012.

6. **Plunkett, LM.** Regulatory primer for pharmacy students: focus on human therapeutics. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

7. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Texas A&M University, College of Pharmacy, Kingsville, TX, May 1, 2009.

8. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Drexel University School of Law. September 22 and 24, 2008.

9. **Plunkett, LM.** Novelty requirement of §102. Lecturer at Rutgers School of Law, Camden Campus. September 22 and 24, 2008.

10. **Plunkett, LM.** Discussion of the Adequacy of Current Regulatory Risk Assessment Approaches for Protection of Children's Health and the Health of Other "Sensitive" Human Subpopulations. Testimony before the U.S. Senate Enviornment and Public Works Committee. April, 29, 2008.

11. **Plunkett, LM.** Strategies for reducing adverse drug reactions: Science versus regulatory considerations. Invited speaker for the AAPS Visiting Scientist Program, Florida A&M University, Tallahassee, FL, October 26, 2006.

12. **Plunkett, LM**. The guidance as currently implemented: experience with Minnesota's draft risk levels. Presented at the ISRTP workshop entitled: EPA's New (Proposed) Guidance for Assessing Cancer Risks from Early Life Exposures. Genotoxic Mode of Action and Implications for Human Health-Based Standards. Baltimore, MD February 10, 2005.

13. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 17, 2004.

14. **Plunkett, LM**. Moderator of the symposium entitled "Regulation of genetically modified cells, foods, organisms and animals for consumer and therapeutic use. Meeting of the American Association of Pharmaceutical Sciences (AAPS), Baltimore, MD, November 11, 2004.

15. **Plunkett, LM**. A Road map to the US Food And Drug Administration Regulations. Invited Speaker and Session Co-chair, Federation of European Biochemical Societies (FEBS), Istanbul, Turkey, October 20-24, 2002.

16. **Plunkett, LM.** An overview of the regulation of products of biotechnology: Who's in charge? Lecturer at University of Houston at Clearlake, November 2001.

17. **Plunkett, LM** . Differences and Similarities Between Children and Adults in their Exposure and Response to Environmental Chemicals: An Update Since 1992. Invited Speaker at ToxForum, Aspen CO, July 2001.

18. **Plunkett, LM**. Do current FIFRA guideline tests protect infants and children? Lead as a case study. Invited speaker at the Sixteenth International Neurotoxicology Conference, Pesticides and Susceptible Populations: Who is at Risk and When? Little Rock, Arkansas, September 13-16 1998

19. **Plunkett, LM**. An overview of biotechnology regulations: the USFDA and the USEPA. Lecturer at University of Houston at Clearlake, October 16 1998.

20. Rodricks, JV, Santamaria, AB, **Plunkett, LM**. Risk Assessment as a Tool in Litigation: A Discussion of the Uses and Their Limits [Presented by **Plunkett LM**]. Society for Risk Analysis, , New Orleans, LA. December 10 1996.

21. **Plunkett, LM**. Current Issues in Lead Exposure and Risk Assessment. Symposia at the annual meeting of The American College of Toxicology, Valley Forge, PA. November 9 1996.

22. **Plunkett, LM** . An Overview of Biotechnology Regulations: Environmental Regulations. Lecturer at the South Texas School of Law, October 1995.

23. **Plunkett, LM**. An Overview of Biotechnology Regulations: FDA Regulations. Lecturer at the South Texas School of Law, October 1995.

24. **Plunkett, LM** . A Discussion of Toxicokinetics. Featured speaker at a symposium at the Int. Congress of Toxicol., July 5 1995.

25. **Plunkett, LM**. Chutes and Ladders: The Hazardous Journey for R&D to Market. Featured speaker at the Futurist's Conference, Irvine, CA, June 28, 1995.

BOOK CHAPTERS

1. Rudenko, L, **Plunkett, LM**, Kornum, A, Rocklinsberg, H, Sorensen, DB, Gjerris, M. 2024. An overview of the regulation of genetically altered animals in research. In: *Biotech Animals in Research: Ethical and Regulatory Aspects*. CRC Press: Boca Raton. Chapter 3.

2. Anderson, SA, **Plunkett, LM.** 2023. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

3. Anderson, SA, **Plunkett, LM.** 2022. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

4. Anderson, SA, **Plunkett, LM**. 2021. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

5. Anderson, SA**, Plunkett, LM.** 2020. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

6. Anderson, SA, **Plunkett, LM.** 2019. Defending Pesticides in Litigation. Thomson Reuters, Eagan, MN.

7. **Plunkett, LM**, O'Donnell, JT. 2016. Ketorolac abuse and injury in college athletics. In: *O'Donnell's Drug Injury, Fourth Edition*. O'donnell and O'Donnell (eds.), Lawyers & Judges Publishing Company, Inc: Tucson, AZ, pp. 591-602.

8. **Plunkett, LM,** Timmerman, LE. 2011. Pharmacovigilance and Postmarket Surveillance in the United States: The Role of the U.S. Food and Drug Administration. In: Elements of Pharmacovigilance: Be Vigilant, Be Safe. R. Sehgal *et al.* (Eds.), Kongposh Publications: New Dehli.

9. Rodricks, JV, Frankos, VH, **Plunkett, LM**. 1995. Food Additives. In: Regulatory Toxicology. C.P. Chengelis, J.F. Holson and S.C. Gad (eds.) Raven Press, New York, New York, 51-82.

10. **Plunkett, LM**, Turnbull, D, Rodricks, JV. 1992. Differences between adults and children affecting exposure assessment. In: Similarities and Differences Between Children and Adults: Implications for Risk Assessment. P.S. Guzelian, C.J. Henry and S.S. Olin (eds.) ILSI Press, Washington D.C., 79-96.

11. Saavedra JM, **Plunkett LM**, Correa FMA, Israel A, Kurihara M, Shigematsu K. 1986. Quantitative autoradiography of angiotensin and atrial natriuretic factor binding sites in brain nuclei of spontaneously hypertensive rats. In Brain Peptides and Catecholamines in Cardiovascular Regulation in Normal and Disease States.

MISCELLANEOUS

1. **Plunkett LM.** 2008. U.S. Senate Committee on Environment & Public Works. Oral testimony. Full Committee hearing entitled "Oversight on EPA Toxic Chemical Policies". Tuesday, April 29, 2008.

2. **Plunkett LM**, Brett SM. 1991. A new look at lead: sources, exposures, and uptake in populations at risk. ENVIRON Report. 5:6-9.

3. **Plunkett LM**, Frankos VH. 1991. FDA re-examines the safety of silicone gel-filled breast implants. ENVIRON Report. 5:10-13.

APPENDIX B

Trial List

List of Testimony for Dr. Laura M. Plunkett, Ph.D, DABT

Year	Case Name	Law Firm Represented
2018	*Cell Phone Litigation* *Deposition Testimony* *November 15, 2018*	Lundy, Lundy, Soileau & South (Lake Charles, LA)
2018	*Gadolinium* *Kish v. GE Electric* *Deposition Testimony* *27 November 2018*	Power Rogers & Smith, PC
2018	*Taxotere* *Deposition Testimony* *10 December 2018*	The Lambert Law Firm (New Orleans, LA)
2018	*Talc* *Brower case Georgia* *Deposition* *18 December 2018*	Beasley Allen (Montgomery, AL)
2018	*Talc MDL* *Deposition* *19 December 2018*	Ashcraft & Gerel LLP (Alexandria, VA)
2019	*Pradaxa Litigation* *Supplemental Deposition* *07 Janaury 2019*	The Nemeroff Firm (Dallas, TX)
2019	*Kubicki v. Medtronic, Inc. et al* *Deposition* *06 March 2019*	Ashcraft & Gerel LLP (Alexandria, VA)
2019	*McCants v. Vitacost, Inc.* *Trial Testimony* *29 March ; 01 April 2019*	Miller Weisbrod (Dallas, TX)

Year	Case Name	Law Firm Represented
2019	*Daniels-Feasel et al v. Forest Pharmaceuticals, Inc., et al* *Deposition* *12 April 2019*	Nidel & Nace PLLC (Washington, DC)
2019	*Taxotere* *Deposition* *22 April 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Pradaxa Litigation* *Ridings v. BIPI* *27 April 2019*	Humphreys, Farrington & McClain (Independence, MO)
2019	*Roberto v. BIPI* *Trial Testimony* *1-3 May 2019*	Ury, Moskow (Fairfield, CT)
2019	*Emley, Donna v. Wal-Mart Stores, Inc., et al.* *Deposition* *14 May 2019*	Childers, Schlueter & Smith (Atlanta, GA)
2019	*Ruiz v. TEVA, et al* *Deposition* *10 June 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)
2019	*Pleasant v. Wellington Regional Med Ctr, et al.* *Deposition* *02 July 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)
2019	*Thomas, et al. v. Mobil Oil Corp, et al* *Deposition* *10 July 2019*	Fransen & Hardin, PLC (New Orleans, LA)
2019	*Ruiz v. TEVA, et al* *Deposition (continuation of 10 June deposition)* *31 July 2019*	Searcy, Denney, Scarola, Barnhart & Shipley (West Palm Beach, FL)
2019	*Coleman case (Cook Medical)* *Deposition* *01 August 2019*	Matthews & Associates (Houston, TX)

Year	Case Name	Law Firm Represented
2019	*Talc* *Brower case Georgia (J&J)* *Trial* *12-16 September 2019*	Beasley, Allen (Montgomery, AL)
2019	*Taxotere MDL* *Trial* *18 September 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Lilla v. Cordis Corporation* *Deposition* *16 October 2019*	Freese & Goss (Dallas, TX)
2019	*Ridings v. BIPI* *Hearing* *28-29 October 2019*	Humphreys, Farrington & McClain (Independence, MO)
2019	*Lilla v. Cordis Corporation* *Deposition (CONTINUATION)* *31 October 2019*	Freese & Goss (Dallas, TX)
2019	*Seegert, et al. V. Rexall Sundown, Inc.* *Deposition* *06 November 2019*	Blood Hurst & O'Reardon, LLP (San Diego, CA)
2019	*Six v. CSX Corporation* *Deposition* *11 November 2019*	Franklin Law, LLC (Savannah, GA)
2019	*Cadigan v. Johnson & Johnson (Talc)* *Deposition* *13 November 2019*	Beasley Allen (Montgomery, AL)
2019	*Crayton & Thibodeaux case (Taxotere)* *Deposition* *19 November 2019*	David F. Miceli, LLC (Carrollton, GA)
2019	*Lyons v. BIPI (Pradaxa)* *Deposition* *25 November 2019*	Ury, Moskow (Fairfield, CT)

Year	Case Name	Law Firm Represented
2019	*Forrest v. Johnson & Johnson (Talc)* *Trial Testimony* *06, 09-10 December 2019*	Beasley Allen (Montgomery, AL)
2019	*Crayton & Thibodeaux case (Taxotere)* *Deposition (**CONTINUATION**)* *13 December 2019*	David F. Miceli, LLC (Carrollton, GA)
2020	*McDermitt case* *Deposition* *21 January 2020*	Goldenberg Law, PLLC (Minneapolis, MN)
2020	*Benitez v. Dr. Ronald Seguar* *Deposition* *23 January 2020*	Orrill & Malbrough, LLC (Metairie, LA)
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *21 February 2020*	Baron and Budd (Encino, CA)
2020	*Kahn case (Taxotere)* *Deposition* *27 April 2020*	David F. Miceli, LLC (Carrollton, GA)
2020	*Sandra Sutter v. Cordis (IVC)* *Deposition* *27 May 2020 and 8 June 2020*	Blankenship Law Firm (Dallas, TX)
2020	*Roney v. Provient* *Deposition* *20 July 2020*	Smith, LaCien LLP (Chicago, IL)
2020	*Taxotere 505b2 Cases* *03 & 08 September 2020*	David F. Miceli, LLC (Carrollton, GA)
2020	*State of Hawai'i (Clare E. Connors, Attorney General) v. Bristol-Myers Squibb (BMS) et al.* *Trial* *26-27 October 2020*	Baron and Budd (Encino, CA)

Year	Case Name	Law Firm Represented
2021	*Kahn case (Taxotere)* *Deposition* *7 April 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Cadigan v. Johnson & Johnson (Talc)* *Trial Testimony* *14-16 July 2021*	Beasley Allen (Montgomery, AL)
2021	*Talc MDL* *Deposition* *10 August 2021*	Ashcraft & Gerel LLP (Alexandria, VA) Beasley Allen (Montgomery, AL)
2021	*Kleiner v. Johnson & Johnson (Talc)* *Trial Testimony* *18-20 and 23-24 August 2021*	Beasley Allen (Montgomery, AL)
2021	*Geise et al. v. Johnson & Johnson (Talc)* *Trial Testimony* *10, 13-14 September 2021*	Beasley Allen (Montgomery, AL)
2021	*Guilbault and Plaisance v. 505b2 Defendants* *Deposition* *24 September 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*Kahn v. Sanofi Aventis* *Trial Testimony* *12 November 2021*	David F. Miceli, LLC (Carrollton, GA)
2021	*State of New Mexico v. Bristol-Myers Squibb (BMS) et al.* *Deposition* *19 November 2021*	Baron & Budd (Encino, CA)
2021	*Mooneyham v. Bactolac* *9 December 2021*	Beasley Allen (Montgomery, AL)
2022	*Earnest case (Taxotere)* *Deposition* *01 June 2022*	David F. Miceli, LLC (Carrollton, GA)

Year	Case Name	Law Firm Represented
2023	*Valsartan MDL* *Deposition* *12 January 2023*	Levin, Papantonio (Pensacola, FL) Hollis Firm (Kansas City, KS)
2023	*Valsartan MDL* *Deposition (continued)* *10 February 2023*	Levin, Papantonio (Pensacola, FL) Hollis Firm (Kansas City, KS)
2023	*Earnest case (Taxotere)* *Deposition (Continuation)* *28 March 2023*	Milberg Coleman (Knoxville, TN)
2023	*Norwood v. Albertson's Inc.* *Deposition* *17 May 2023*	Lundy. Soileau (Lake Charles, LA)
2023	*Jackson v. Bayer HealthCare* *Pharmaceuticals Inc., et al.,* *20 July 2023*	Yerrid Law (Tampa, FL)
2023	*State of Hawai'i (Attorney General) v. Bristol-* *Myers Squibb (BMS) et al.* *Deposition* *29 August 2023*	Baron & Bud (Encino, CA)
2023	*State of Hawai'i (Attorney General) v. Bristol-* *Myers Squibb (BMS) et al.* *Trial* *25, 29 September and 2 October 2023*	Baron & Bud (Encino, CA)
2023	*Blakely, et al v. Lifecell* *Deposition* *19 October 2023*	Cohen Malad (Indianapolis, IN)

Year	Case Name	Law Firm Represented
2023	*Mississippi AG v. Johnson & Johnson (Talc)* *Deposition* *24 October 2023*	Beasley Allen (Montgomery, AL)

APPENDIX C

List of Materials and Data Considered

Documents

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CYWM-MA60523-0001

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PCPC0082712
PCPC0082720
PCPC0082732
PCPC-MDL00141419
RJLEE001497
WIND-MA10764
WTALC00008273

Transcripts

Deposition testimony and exhibits of Linda Loretz, January 8, 2016

Deposition testimony and exhibits of Mark Pollak, February 18, 2016

Deposition testimony and exhibits of John Poston, September 27, 2012

Deposition testimony and exhibits of Shripal Sharma, September 26, 2012

Deposition testimony and exhibits of Gary Rosenthal, Ph.D., June 11, 2015

Deposition testimony and exhibits of Curtis Omiecinski, Ph.D., May 20, 2015

Deposition testimony and exhibits of Dr. Graham Colditz, October 16, 2015

Testimony and referenced materials of Dr. Graham Colditz, August 16, 2016 (Kemp Hearings)

Testimony and referenced materials of Dr. Omiecinski, August 15, 2016 (Kemp Hearings)

Testimony and referenced materials of Dr. Chodosh, August 19, 2016 (Kemp Hearings)

Trial testimony and exhibits of David Steinberg, Volume 4A, April 13, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of David Steinberg, Volume 4B, April 13, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of David Steinberg, Volume 5A, April 14, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of David Steinberg, Volume 5B, April 14, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of Lorena Telofski, Volume 7B, April 18, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of Lorena Telofski, Volume 8A, April 19, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of David Steinberg, Volume 9B, April 20, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of Shipral Sharma, Volume 10, April 21, 2016, Ristesund v. Johnson & Johnson, et al.

Volume 16, April 29, 2016, Ristesund v. Johnson & Johnson, et al.

Trial testimony and exhibits of Susan Nicholson, October 24-25, 2016; February 24, 27- 28, 2017; March 1, 2017

Deposition testimony and exhibits of Susan Nicholson, July 26-27, 2018

Deposition testimony and exhibits of Patrick Downey, August 7-8, 2018

Deposition testimony and exhibits of Tina French, August 15, 2018

Deposition testimony and exhibits of Robert Glenn, October 18, 2018

Deposition testimony and exhibits Margaret Gurowitz, July 12, 2018

Deposition testimony and exhibits of Donald Hicks, June 28-29, 2018

Deposition testimony and exhibits of John Hopkins, October 19, 2012; August 16-17, 2018; October 17, 2018; November 5, 2018

Trial testimony and exhibits of John Hopkins, February 8, 12-14, 20, 2018

Trial testimony of Juan Felix, MD, Berg v. Johnson & Johnson, Volume 5, Septemer 30, 2013

Deposition testimony and exhibits of Linda Loretz, July 17, 2018; October 1-2, 2018

Deposition testimony and exhibits of Joseph Muscat, September 25, 2018

Deposition testimony and exhibits of Julie Pier, September 12-13, 2018

Deposition testimony and exhibits of Mark Pollak, August 29, 2018

Deposition testimony and exhibits of Alice Blount, April 13, 2018

Deposition testimony and exhibits of Aviam Elkies, December 15, 2016

Deposition testimony and exhibits of William Longo, August 23, 2017

Trial testimony and exhibits of William Longo, May 15-16, 2018; February 20, 2018; June 7, 2018

Deposition testimony and exhibits of David Madigan, February 6, 2018; March 13, 2018

Trial testimony and exhibits of Alan Andersen, August 10-11, 2018

Deposition testimony and exhibits of Alan Andersen, August 18, 2017

Trial testimony and exhibits of Karen Boehler, October 26, 2016

Trial testimony of Dr. John Hopkins, February 8, 2018

Deposition testimony of Dr. Susan Nicholson, July 26, 2018

Deposition testimony of Dr. Linda Loretz, July 17, 2018

Trial testimony of Dr. Alan Andersen and trial exhibits, August 11, 2017

Deposition of Bruce Semple, November 6, 1984

Deposition and exhibits of Joanne Waldstreicher, MD April 19, 2017

Deposition and exhibits of Alex Gorsky, October 3, 2019

Trial testimony and exhibits of Alex Gorsky, January 27, 2020 Barden, et al v. Brenntag, et al.

Deposition testimony and exhibits of Steven Mann, April 8, 2021 and April 28, 2021

Deposition testimony and exhibits of Timothy McCarthy, May 20, 2021

Deposition testimony and exhibits of Susan Nettesheim, April 16, 2021

Deposition testimony and exhibits of Lorena Telofski, February 24, 2021

Deposition testimony and exhibits of Kathleen Wille, April 13, 2021, April 26, 2021 and June 7, 2021

Trial Exhibits

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P-0760	
P-0771	
P-0787	

P-0816

P-0820

P-0880

P-0881

D-7

DX-1097

Miscellaneous

United States Patent No. 4,474,742, filed February 17, 1983 and issued October 2, 1984

United States Patent No. 2,626,257 filed May 21, 1952 and issued November 23, 1953

U.S. Patent and Trademark Office. "Powder Lubricated Surgeons Rubber Glove." US. Patent No. 2,621,333. Dec. 16, 1952.

U. S. Patent Office. "Medical Dusting Powder." U.S. Patent No. 2,626,257. Jan. 20, 1953.

40 Federal Register 40(42) March 3, 1975

Federal Register. Asbestos; Reporting and Recordkeeping Requirements Under the Toxic Substances Control Act (TSCA). A Final Rule by the EPA on July 25, 2023.

21 CFR 740

57 FR 3129, Jan. 28, 1992

21 CFR 720

39 FR 10059, Mar. 15, 1974; 21 CFR 710

39 FR 10056, Mar. 15, 1974; 21 CFR 701

21 CFR 201.57

21 CFR 740.1

21 CFR Part 10

Talc, MSDS, February 26, 2009

Talc, MSDS, June 1, 2003

Talc, MSDS, June 1, 2007

Talc, MSDS, October 1, 1996

CIR Procedure

Cosmetic Labeling Guide

Environmental Health Criteria 235, Dermal Absorption (WHO) 2006.

RoC Handbook for Preparing Reports on Monographs

Presentation presented by John M. DeSesso, Ph.D., dated January 18, 2018, Toxic Talc? Anatomy of a Talc Defense

AMA Analytical Services, Inc., Certificate of Analysis, revised October 11, 2019

State of California Environmental Protection Agency Office of Environmental Health Hazard Assessment Safe Drinking Water and Toxic Enforcement Act 1986 "Chemicals Known to the State to Cause Cancer or Reproductive Toxicity" January 27, 2017

The California Safe Cosmetics Act 2005, April 15, 2015

National Toxicology Program (NTP), Summary Minutes, Dec. 13-15, 2000

Letter from Steven M. Musser. FDA to Samuel Epstein CPC, April 1, 2014

Letter from John Bailey, Jr. Ph.D. to Jill Cashen, response to citizen petition, July 11, 1995

Letter from PCPC Comments on Petition from John Bailey, July 21, 2009

Congressional Research Service (CRS). 2012. FDA Regulation of Cosmetics and Personal Care Products. R42594. July 9.

Rio Tinto Minerals Analytical Group 2010, (2010).

Talc & Asbestos - Broughton Project and NTP, (2000).

Development of a New ASTM Method for the Analysis of Cosmetic and Pharmaceutical Talc for Asbestos, (2011).

J&J audit RJ Lee, Chrysotile detected in J&J sample (2016).

Toxicology and Exposure Guidelines Chemical Safety | Environmental Health & Safety | Nebraska, , https://ehs.unl.edu/documents/chemical-safety (last visited Aug 29, 2018).

Hearings Before the Environment Subcommittee of the Committee on Commerce United States Senate, February 23, 26 and March 21, 1973

ISSCAN database on chemical carcinogens

July 2011, Powerpoint Presentation, Development of a New ASTM Method for the Analysis of Cosmetic and Pharmaceutical Talc for Asbestos, Johnson Conference

Report of Evaluation of Cosmetics and Cosmetic Talc for FDA, Daniel Crane, February 23, 2019

Final screening assessment of talc under the Chemicals Management Plan, April 2021

Health Canada Infographic, April 2021

Talc: Health risks associated with inhalation and exposure to the female genital area, April 2021

Screening Assessment. Talc. Chemical Abstracts Servce Registry Number 14807-966. Environment and Climate Change Canada. Health Canada. April 2021

FDAFOIA 000001 - 694

Safe for use list S-062016posted072016

Safe with qualifications list SQ-062016posted072016

Unsafe for use list U-062016posted072016

_11.17.94 - CPC Cit Pet re talc and OVCA

Harlow Cramer et al. Perineal exposure to talc and ov cancer risk (1992)

Egli and Newton - 1961 - The transport of carbon particles in the human fem

Venter Iturralde. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries (1979)

Henderson Hamilton et al. The demonstration of the migration of talc from the vagina...(1986) - IMERYS080187

Newhouse et al. A study of the mortality of female asbestos workers (1972) - IMERYS-A_0000310

Wignall and Fox - 1982 - Mortality of female gas mask assemblers

Acheson et al. - 1982 - Mortality of two groups of women who manufactured

Cralley et al. Fibrous and mineral content of cosmetic talcum products (1968) - JNJ000308811

Rohl et al. Consumer talcums and powders - mineral and chemical characterization (1976) - IMERYS-A_0002343

NTP Technical Report 421 September 1993 (NIH Publication 93-3152)

Hartge Lesher. Talc and OVCA)1983) - JNJ000013131

Rosenblatt Szklo Rosenshein. Mineral fiber exposure and the development of OVCA (1992) - IMERYS080307

Whittmore Wu et al. Personal and environmental characteristics related to epithelial OVCA (1988) - JNJ000004870

Cramer et al Ovarian cancer and talc-a case-control study (1982)

5.13.08 - Cit Petition, CPC (Talc)

SEER Cancer Statistics Review, 1975-2005

Purdie Green et al. Reproductive and other factors and risk of epithelial OVCA...(1995) - JNJ000004975

Kasper Chandler. Possible morbidity in women from talc on condoms (1995) - JNJ000016672

Cramer Xu. Epidemiologic evidence for uterine growth factors...(1995) - IMERYS038009

Chang Risch. Perineal talc exposure and risk of ov carcinoma (1997)

Daly Obrams. Epidemiology and risk assessment for OVCA (1998) - IMERYS038018

Green Purdie et al. Tubal sterilisation, hysterectomy and decreased risk of ov cancer (1997)

Cramer Liberman et al. Genital talc exposure and risk of ovarian cancer (1999)

Huncharek Geschwind Kupelnick. Perineal application of cosmetic talc and risk of invasive...(2003) - IMERYS051453

Baan Straif et al. Carcinogenicity of carbon black, titanium dioxide and talc (2006) - IMERYS080117

Langseth et al. Perineal use of talc and risk of ov cancer (2007)

Merritt et al. Talcum powder, chronic pelvic inflammation and NSAID...(2008)

2009-2010, FDA Survey on Talc Safety

Report and supporting materials of Dr. Chodosh

Report and supporting materials of F. Alan Andersen, Giannecchini v. Johnson & Johnson, et al.

Report and supporting materials, Dr. Cramer, Blaes v. Johnson & Johnson, et al.

Report and supporting materials, Dr. Omiecinski, Blaes v. Johnson & Johnson, et al.

Report and supporting materials, Dr. Godleski, Blaes v. Johnson & Johnson, et al.

Report and supporting materials, Dr. Ness, Blaes v. Johnson & Johnson, et al.

Report and supporting materials, David Steinberg, Blaes v. Johnson & Johnson, et al.

Expert Report of Samuel Cohen_Giannecchini

Expert Report of Susan Nicholson_Giannecchini

Expert Report of William Allaban_Giannecchini

Report and supporting materials, Dr. Rosenthal, Blaes v. Johnson & Johnson, et al.

Educational Report and supporting materials of Dr. Thomas Dydek, dated April 9, 2018

Report and supporting materials of Dr. Thomas Dydek, dated August 16, 2018

Report and supporting materials of Dr. Michael Crowley, dated November 12, 2018

Report and supporting materials of Dr. William E. Longo and Dr. Mark Rigler, dated February 28, 2017

Report and supporting materials of Dr. William E. Longo and Dr. Mark Rigler, dated August 2, 2017

Report and supporting materials of Dr. William E. Longo and Dr. Mark Rigler, dated September 2017

Report and supporting materials of Dr. William E. Longo and Dr. Mark Rigler, dated February 16, 2018

Report and supporting materials of Dr. William E. Longo and Dr. Mark Rigler, dated November 14, 2018

Report and supporting materials of Dr. David Madigan, dated January 1, 2018

Amended Expert Report and supporting materials of Robert B. Cook, Ph.D., January 22, 2019

Expert report dated August 2, 2017 prepared by William Longo and Mark Rigler of the Materials Analytical Services (MAS) laboratory entitled "Analysis of Johnson & Johnson Baby Powder & Valiant Shower to Shower Talc Products for Amphibole (Tremolite) Asbestos

Expert report dated September 2017 prepared by William Longo, Mark Rigler, and William Egeland of the Materials Analytical Services (MAS) laboratory entitled “Below the Waist Application of Johnson & Johnson Baby Powder”.

The Analysis of Johnson & Johnson’s Historical Product Containers and Imerys’ Historical Railroad Car Samples from the 1960s to the Early 2000s for Amphibole Asbestos, 2nd Supplemental Report, Longo & Rigler, MAS Analytical Services, February 1, 2019

Defendant Johnson & Johnson Consumer Inc.’s Supplemental Answer to Plaintiffs’ Second Set of Interrogatories. No. 19

Attorneys Eyes Only, Exhibit 1, Exhibit 2 and Exhibit 3

Defendants Motion to Exclude re General Causation

Defendants Motion to Exclude re Specific Causation

Defendants Motion to Exclude Steinberg

5.19.16 - Opp to PCPC MTC, Anti-SLAPP

Points and Authority for Opp to PCPC Anti-Slapp

9.2.16 - Kemp Hearing Final Opinion & Order

Civil Administrative Subpoena to Gene Williams, July 30, 2013

https://www.canada.ca/en/health-canada/services/chemicals-product-safety/talc.html

https://www.canada.ca/en/health-canada/services/chemicals-substances/fact-sheets/chemicals-glance/talc.html

https://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2018/68320a-eng.php

News Publications

Press Release, 15 New Tests from the Same Bottle of Johnson’s Baby Powder Previously Tested by FDA Find No Asbestos, Johnson & Johnson Consumer, Inc., October 29, 2019

Terhune, et al., Exclusive: J&J’s own expert working for FDA, found asbestos in Baby Powder, Reuters, October 30, 2019

Johnson & Johnson Consumer Inc. to Voluntarily Recall a Single Lot of Johnson’s Baby Powder in The United States, October 18, 2019

Rogers, Charlotte, Johnson & Johnson is rebranding its entire baby care portfolio, prioritizing transparency over science as it looks to get closer to parents, June 27, 2018

Dyer, Owen, Johnson & Johnson recalls its Baby Powder after FDA finds asbestos in sample, BMJ, October 21, 2019

Odell, Patty, J&J Consumer Takes Strong Steps to Revitalize its Brand, October 30, 3018

Tirrell, Meg, Johnson & Johnson to relaunch baby-care line after its 20% sales decline, May 16, 2018

Ghio, et al., Talc Should not be Used for Pleurodesis in Patients with Nonmalignant Pleural Effusions, 2001

FDA Advises Consumers to Stop Using Certain Cosmetic Products, October 18, 2019

News release: Government of Canada Assessment Concludes that Talc May be Harmful to Human Health April 22, 2021

Press Release, Johnson & Johnson Consumer Health announces discontinuation of talc-based Johnson's Baby Powder in U.S. and Canada, May 19, 2020. https://www.jnj.com/our-company/johnson-johnson-consumer-health-announces-discontinuation-of-talc-based-johnsons-baby-powder-in-u-s-and-canada

Press Release, Johnson & Johnson Consumer Health to Transition Global Baby Powder Portfolio to Cornstarch, August 11, 2022. https://www.jnj.com/johnson-johnson-consumer-health-to-transition-global-baby-powder-portfolio-to-cornstarch#:~:text=August%2011%2C%202022%20%E2%80%93%20%22As,be%20discontinued%20globally%20in%202023.

Medical Literature

Anon. 2000. The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. Inhal.Toxicol. 12(1-2):1-17.

Abraham, J. L. and D. D. McEuen. 1986. Inorganic particulates associated with pulmonary alveolar proteinosis: SEM and X-ray microanalysis results. Appl.Pathol. 4(3):138-146.

Acheson, E. D. et al. 1982. Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. Br.J Ind.Med. 39(4):344-348.

Adamson, I. Y. and H. Prieditis. 1998. Silica deposition in the lung during epithelial injury potentiates fibrosis and increases particle translocation to lymph nodes. Exp.Lung Res 24(3):293-306.

Afzal, M., Saleem, S., Singh, N., Kazmi, I., Khan, R., Nadeem, M. S., … Anwar, F. (2018). Evaluation of diphenhydramine in talc induced type 2 diabetes mellitus in Wistar rats. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie, 97, 652–655. https://doi.org/10.1016/j.biopha.2017.10.085

Alexander, N. J., Baker, E., Kaptein, M., Karck, U., Miller, L., & Zampaglione, E. (2004). Why consider vaginal drug administration? Fertility and Sterility, 82(1), 1–12. https://doi.org/10.1016/j.fertnstert.2004.01.025

Allison, A. C. (1978). Interactions of Silica and Asbestos with Macrophages. In G. Bendz, I. Lindqvist, & V. Runnström-Reio (Eds.), Biochemistry of Silicon and Related Problems (pp. 337–356). Boston, MA: Springer US. https://doi.org/10.1007/978-1-4613-4018-8_16

Allison, A. C., Harington, J. S., & Birbeck, M. (1966). An examination of the cytotoxic effects of silica on macrophages. The Journal of Experimental Medicine, 124(2), 141–154.

Anderson, E. L. et al. 2017. Assessment of Health Risk from Historical Use of Cosmetic Talcum Powder. Risk Anal. 37(5):918-929.

Antony, V. B., Nasreen, N., Mohammed, K. A., Sriram, P. S., Frank, W., Schoenfeld, N., & Loddenkemper, R. (2004). Talc pleurodesis: basic fibroblast growth factor mediates pleural fibrosis. Chest, 126(5), 1522–1528. https://doi.org/10.1378/chest.126.5.1522

Arellano-Orden, E. et al. 2013. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. Respiration 86(3):201-209.

ATSDR. 2001. Toxicological profile for asbestos. Agency for Toxic Substances and Disease Registry, Division of Toxicology/Toxicology Information Branch.

Axelson, O. et al. 2003. Re: Regulatory Toxicology and Pharmacology. Int J Occup.Environ.Health 9(4):386-389.

Baiu, I. et al. 2019. Talc Pleurodesis: a Medical, Medicolegal, and Socioeconomic Review. Ann Thorac.Surg.

Baker, T. R., & Piver, M. S. (1994). Etiology, biology, and epidemiology of ovarian cancer. Seminars in Surgical Oncology, 10(4), 242–248.

Barlow, C. A., Marsh, G. M., Benson, S., & Finley, B. L. (2018). The mineralogy and epidemiology of cosmetic talc. Toxicology and Applied Pharmacology. https://doi.org/10.1016/j.taap.2018.05.036

Barlow, C. A., Sahmel, J., Paustenbach, D. J., & Henshaw, J. L. (2017). History of knowledge and evolution of occupational health and regulatory aspects of asbestos exposure science: 1900-1975. Critical Reviews in Toxicology, 47(4), 286–316. https://doi.org/10.1080/10408444.2016.1258391

Beck, B. D. et al. 1987. The pulmonary toxicity of talc and granite dust as estimated from an in vivo hamster bioassay. Toxicol.Appl.Pharmacol. 87(2):222-234.

Beck, B.D. et al. 1982. An in vivo hamster bioassay to assess the toxicity of particulates for the lungs. Toxicol.Appl Pharmacol. 66(1):9-29.

Berge, W. et al. 2018. Genital use of talc and risk of ovarian cancer: a meta-analysis. Eur.J Cancer Prev. 27(3):248-257.

Berger, M. and Berger, B. A. 2017. FDA and related regulatory agencies In: Fundamentals of US Regulatory Affairs, 10th edition. Pamela A.Jones, Senior Editor, Regulatory Affiars Professionals Society: Rockville, MD, chapter 1.

Berry, G., Newhouse, M. L., & Wagner, J. C. (2000). Mortality from all cancers of asbestos factory workers in east London 1933-80. Occupational and Environmental Medicine, 57(11), 782–785.

Bhattacharjee, P., Paul, S., & Bhattacharjee, P. (2016). Risk of occupational exposure to asbestos, silicon and arsenic on pulmonary disorders: Understanding the genetic-epigenetic interplay and future prospects. Environmental Research, 147, 425–434. https://doi.org/10.1016/j.envres.2016.02.038

Birchall, J. D., & Espie, A. W. (1986). Biological implications of the interaction (via silanol groups) of silicon with metal ions. Ciba Foundation Symposium, 121, 140–159.

Blejer, H. P. and R. Arlon. 1973. Talc: a possible occupational and environmental carcinogen. J.Occup.Med. 15(2):92-97.

Blount, A. M. 1991. Amphibole content of cosmetic and pharmaceutical talcs. Environ.Health Perspect. 94:225-230.

Blount, A. M. & A. H. Vassiliou, Identification of chlorite and serpentine in cosmetic or pharmaceutical talc, 51 Environ. Health Perspect. 379–385 (1983).

Bluemel, G., F. Piza, and W. Zischka-Konorsa. 1962. [Experimental animal research on the tissue reaction to starch and talc powder after their intraperitoneal use]. Wien.Klin.Wochenschr. 74:12-13.

Bluemel, Piza, & Zischka-Konorsa, W. (1962). Animal experimental investigations of tissue reactions to starch and talcum powder after intraperitoneal application. Wiener klinische Wochenschrift, 74(1).

Blumenkrantz, M. J. et al. 1981. Retrograde menstruation in women undergoing chronic peritoneal dialysis. Obstet.Gynecol. 57(5):667-670.

Boorman, G. A., & Seely, J. C. (1995). The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regulatory Toxicology and Pharmacology: RTP, 21(2), 242–243. https://doi.org/10.1006/rtph.1995.1035

Booth, M., V. Beral, and P. Smith. 1989. Risk factors for ovarian cancer: a case-control study. Br.J Cancer 60(4):592-598.

Boutwell, R. K. (1985). Tumor promoters in human carcinogenesis. Important Advances in Oncology, 16–27.

Brandenberger, C. et al. 2015. Assessing particle and fiber toxicology in the respiratory system: the stereology toolbox. Part Fibre.Toxicol. 12:35

Brouillette, F. and M. L. Weber. 1978. Massive aspiration of talcum powder by an infant. Can.Med.Assoc.J 119(4):354-355.

Bulbulyan, M. A. et al. 1999. Cancer mortality among women in the Russian printing industry. Am.J Ind.Med. 36(1):166-171.

Bunderson-Schelvan, M. et al. 2011. Nonpulmonary outcomes of asbestos exposure. J Toxicol.Environ.Health B Crit Rev. 14(1-4):122-152.

Burns, A.M. et al. 2019. Potential Airborne Asbestos Exposure and Risk Associated with the Historical Use of Cosmetic Talcum Powder Products. Risk Anal. 39(10):2272-2294.

Buz'Zard, A. R. and B. H. Lau. 2007. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. Phytother.Res. 21(6):579-586.

Califf, R. M., McCall, J., & Mark, D. B. (2017). Cosmetics, Regulations, and the Public Health: Understanding the Safety of Medical and Other Products. JAMA Internal Medicine, 177(8), 1080–1082. https://doi.org/10.1001/jamainternmed.2017.2773

Camargo, M. C. et al. 2011. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. Environ.Health Perspect. 119(9):1211-1217.

Campos, J. R., Werebe, E. C., Vargas, F. S., Jatene, F. B., & Light, R. W. (1997). Respiratory failure due to insufflated talc. Lancet (London, England), 349(9047), 251–252. https://doi.org/10.1016/S0140-6736(05)64860-X

Carr, C. J. 1995. Talc: Consumer uses and health perspectives. Regulatory Toxicology and Pharmacology 21:211-215.

CDC - Asbestos - NIOSH Workplace Safety and Health Topics. (2018, August 7). Retrieved August 29, 2018, from https://www.cdc.gov/niosh/topics/asbestos/

Casey, R. and T.P. Larkin. 2019. Ovarian Cancer and "Tainted Talc": What Treating Physicians Need to Know. Mo.Med. 116(2):83-86.

Chamberlain, M., & Brown, R. C. (1978). The cytotoxic effects of asbestos and other mineral dust in tissue culture cell lines. British Journal of Experimental Pathology, 59(2), 183–189.

Chang, C.-J., Tu, Y.-K., Chen, P.-C., & Yang, H.-Y. (2017). Occupational Exposure to Talc Increases the Risk of Lung Cancer: A Meta-Analysis of Occupational Cohort Studies. Canadian Respiratory Journal, 2017, 1270608. https://doi.org/10.1155/2017/1270608

Chang, S. and H. A. Risch. 1997. Perineal talc exposure and risk of ovarian carcinoma. Cancer 79(12):2396-2401.

Chen, Y. et al. 1992. Risk factors for epithelial ovarian cancer in Beijing, China. Int.J Epidemiol. 21(1):23-29.

Chirino, O.R. 2019. Tainted Talc and Ovarian Cancer. Mo.Med. 116(3):170-171.

Chouairy, C. J., Hajal, E. A., & Nehme, Y. A. (2012). Xanthogranulomatous oophoritis secondary to talcum powder. Case report and review of the literature. Le Journal Medical Libanais. The Lebanese Medical Journal, 60(3), 169–172.

Chow, E. T., & Mahalingaiah, S. (2016). Cosmetics use and age at menopause: is there a connection? Fertility and Sterility, 106(4), 978–990. https://doi.org/10.1016/j.fertnstert.2016.08.020

Claverie, M., Dumas, A., Carême, C., Poirier, M., Le Roux, C., Micoud, P., … Aymonier, C. (2018). Synthetic Talc and Talc-Like Structures: Preparation, Features and Applications. Chemistry (Weinheim an Der Bergstrasse, Germany), 24(3), 519–542. https://doi.org/10.1002/chem.201702763

Cless, D. and R. Anger. 1954. [Fatal asphyxia caused by aspiration of baby powder]. Kinderarztl.Prax. 22(11):506-508.

Cohen, S. M., Chowdhury, A., & Arnold, L. L. (2016). Inorganic arsenic: A non-genotoxic carcinogen. Journal of Environmental Sciences (China), 49, 28–37. https://doi.org/10.1016/j.jes.2016.04.015

Combes, R. D. (2013). Is phenylbutazone a genotoxic carcinogen? A weight-of-evidence assessment. Alternatives to Laboratory Animals: ATLA, 41(3), 235–248.

Committee on the State of the Science in Ovarian Cancer Research et al., Ovarian Cancers: Evolving Paradigms in Research and Care (2016), http://www.ncbi.nlm.nih.gov/books/NBK367618/ (last visited Aug 29, 2018).

Congressional Research Service. 7-29-2012. FDA regulation of cosmetics and personal care products.

Cook, L. S., M. L. Kamb, and N. S. Weiss. 1997. Perineal powder exposure and the risk of ovarian cancer. Am.J Epidemiol. 145(5):459-465.

Cooke, W. E. 1927. Pulmonary Asbestosis. Br.Med.J 2(3491):1024-1025.

Cosmetic Ingredient Review (CIR). 2013. Safety assessment of talc as used in cosmetics. Final report dated April 12, 2013. Panel meeting date: March 18-19, 2013.

Cosmetic Ingredient Review (CIR). 2016. Quick reference table. http://www.cir-safety.org/supplementaldoc/u-062016posted072016

Cox, M. J., Woods, J. A., Newman, S., & Edlich, R. F. (1996). Toxic effects of surgical glove powders on the eye. Journal of Long-Term Effects of Medical Implants, 6(3–4), 219–226.

Craig, Z. R., & Ziv-Gal, A. (2018). Pretty Good or Pretty Bad? The Ovary and Chemicals in Personal Care Products. Toxicological Sciences: An Official Journal of the Society of Toxicology, 162(2), 349–360. https://doi.org/10.1093/toxsci/kfx285

Cralley, L. J. et al., Source and identification of respirable fibers, 29 Am Ind Hyg Assoc J 129–135 (1968).

Cralley, L. J. et al. 1968. Fibrous and mineral content of cosmetic talcum products. Am.Ind.Hyg.Assoc J 29(4):350-354.

Cramer, D. W. et al. 1982. Ovarian cancer and talc: a case-control study. Cancer 50(2):372-376.

Cramer, D. W. and H. Xu. 1995. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. Ann.Epidemiol. 5(4):310-314.

Cramer, D.W. The Epidemiology of Endometrial and Ovarian Cancer, 26 Hematol Oncol Clin North Am 1–12 (2012).

Cramer, D.W. et al., Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer, 14 Cancer Epidemiol Biomarkers Prev 1125–1131 (2005).

Cramer, D. W. 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet.Gynecol. 94(1):160-161.

Cramer, Daniel W., Titus-Ernstoff, L., McKolanis, J. R., Welch, W. R., Vitonis, A. F., Berkowitz, R. S., & Finn, O. J. (2005). Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer. Cancer Epidemiology Biomarkers & Prevention, 14(5), 1125–1131. https://doi.org/10.1158/1055-9965.EPI-05-0035

Cramer, D. W. et al. 2007. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. Obstet.Gynecol. 110(2 Pt 2):498-501.

Cramer, D. W. et al. 1999. Genital talc exposure and risk of ovarian cancer. Int.J Cancer 81(3):351-356.

Cramer, D. W. et al. 2016. The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States. Epidemiology 27(3):334-346.

Crawford, L., Reeves, K. W., Luisi, N., Balasubramanian, R., & Sturgeon, S. R. (2012). Perineal powder use and risk of endometrial cancer in postmenopausal women. Cancer Causes & Control: CCC, 23(10), 1673–1680. https://doi.org/10.1007/s10552-012-0046-3

Creery, R. D., D. M. McClure, and R. J. Rutherford. 1957. Talc granuloma of the umbilicus. Lancet 272(6970):667-668.

Cygielman, S., & Robson, J. M. (1963). THE EFFECT OF IRRITANT SUBSTANCES ON THE DEPOSITION OF GRANULATION TISSUE IN THE COTTON PELLET TEST. The Journal of Pharmacy and Pharmacology, 15, 794–797.

Daly, M. and G. I. Obrams. 1998. Epidemiology and risk assessment for ovarian cancer. Semin.Oncol. 25(3):255-264.

Darcy, D. A. (1966). Enhanced response of an “acute phase” serum protein to repeated tissue damage in the rat. British Journal of Experimental Pathology, 47(5), 480–487.

Davies, R. et al. 1983. Cytotoxicity of talc for macrophages in vitro. Food Chem.Toxicol. 21(2):201-207.

Davis, C et al. Genital Powder Use and Risk of Epithelial Ovarian Cancer in the Ovarian Cancer in Women of African Ancestry Consortium. Cancer Epidemiol Biomarkers Prev. 2021; 30: 1660-8.

de Boer, C. H. 1972. Transport of particulate matter through the human female genital tract. J Reprod.Fertil. 28(2):295-297.

Ding, D et al. Insights into the Role of Oxidative Stress in Ovarian Cancer. Oxidative Medicine and Cellular Longevity Vol. 2021. https://doi.org/10.1155/2021/8388258.

Doig, A. T. (1949). Other lung diseases due to dust. Postgraduate Medical Journal, 25(290), 639–649, illust.

Doll, R. 1955. Mortality from lung cancer in asbestos workers. Br.J Ind.Med. 12(2):81-86.

Doll, R. (1993). Mortality from lung cancer in asbestos workers 1955. British Journal of Industrial Medicine, 50(6), 485–490.

Doll, R., Peto, R., Wheatley, K., Gray, R., & Sutherland, I. (1994). Mortality in relation to smoking: 40 years’ observations on male British doctors. BMJ : British Medical Journal, 309(6959), 901–911.

Donaldson, K. (2000). Nonneoplastic lung responses induced in experimental animals by exposure to poorly soluble nonfibrous particles. Inhalation Toxicology, 12(1–2), 121–139. https://doi.org/10.1080/08958370050029824

Drechsel, D. A., Barlow, C. A., Bare, J. L., Jacobs, N. F., & Henshaw, J. L. (2018). Historical evolution of regulatory standards for occupational and consumer exposures to industrial talc. Regulatory Toxicology and Pharmacology: RTP, 92, 251–267. https://doi.org/10.1016/j.yrtph.2017.12.005

Dreessen, W. C. (1933). Effects of Certain Silicate Dusts on the Lungs. Journal of Industrial Hygiene, 15, 66–78.

Dreessen, W. C. and J. M. Dalla Valle. 1935. The effects of exposure to dust in two Georgia talc mills and mines. Public Health Reports 50(5):131-143.

Dresler, C. M., Olak, J., Herndon, I., James E., Richards, W. G., Scalzetti, E., Fleishman, S. B., … Sugarbaker, D. J. (2005). Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion*. Chest, 127(3), 909–915. https://doi.org/10.1378/chest.127.3.909

Dyer O. Johnson & Johnson "regrets" 1971 study that injected asbestos into US prisoners BMJ 2022; 376:o681 doi:10.1136/bmj.o681.

Eaton, David L. and Gilbert, Steven G. 2013. Principles of toxicology In: Casarett and Doull's Toxicology, The Basic Science of Poisons, 8th edition. Curtis D.Klaassen, Ph. D., The McGraw-Hill Education: New York, NY, chapter 2.

Eberl, J. J., W. L. George, and . 1948. Comparative evaluation of the effects of talcum and a new absorbable substitute on surgical gloves. Am.J Surg. 75(3):493-497.

Edelstam, G. A., A. C. Sjösten, and H. Ellis. 1997. Retrograde migration of starch in the genital tract of rabbits. Inflammation 21(5):489-499.

Edlich, R. F., Woodard, C. R., Pine, S. A., & Lin, K. Y. (2001). Hazards of powder on surgical and examination gloves: a collective review. Journal of Long-Term Effects of Medical Implants, 11(1–2), 15–27.

Egilman, D., T. Bird, and R. Wilson. 2018. Use of Anti-Warnings to Falsely Reassure Downstream Users: An Asbestos Example. New Solut. 28(3):515-538.

Egilman, D. and J. Steffen. 2018. Commentary on "Assessment of Health Risk From Historical Use of Cosmetic Talcum Powder". New Solut. 28(3):400-409.

Egilman, D. et. al. 2019. Health effects of censored elongated mineral particles: A critical review. ASTM, Int'l.

Egilman, D. et al. 2020. Evidence that cosmetic talc is a cause of ovarian cancer. Gynecol Pelvic Med

Egli, G. E. and M. Newton. 1961. The transport of carbon particles in the human female reproductive tract. Fertil.Steril. 12:151-155.

Eiseman, B., M. G. Seelig, and N. A. Womack. 1947. Talcum Powder Granuloma: A Frequent and Serious Postoperative Complication. Ann.Surg. 126(5):820-832.

Elmes, P. C. (1966). The epidemiology and clinical features of asbestosis and related diseases. Postgraduate Medical Journal, 42(492), 623–635.

Eltabbakh, G. H. et al. 1998. Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet.Gynecol. 91(2):254-259.

Endo-Capron, S., Renier, A., Janson, X., Kheuang, L., & Jaurand, M. C. (1993). In vitro response of rat pleural mesothelial cells to talc samples in genotoxicity assays (sister chromatid exchanges and DNA repair). Toxicology in Vitro: An International Journal Published in Association with BIBRA, 7(1), 7–14.

Ethicon surgical gloves biosorb. (n.d.).

Farber, H. W., Fairman, R. P., Millan, J. E., Rounds, S., & Glauser, F. L. (1989). Pulmonary response to foreign body microemboli in dogs: release of neutrophil chemoattractant activity by vascular endothelial cells. American Journal of Respiratory Cell and Molecular Biology, 1(1), 27–35. https://doi.org/10.1165/ajrcmb/1.1.27

Fernandes, J. V. et al. 2015. The role of the mediators of inflammation in cancer development. Pathol.Oncol.Res. 21(3):527-534.

Ferrante, D. et al. 2017. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. Occup.Environ.Med. 74(12):887-898.

Finkelstein, Murray Martin. (2017). Re: Brent L. Finley, Stacey M. Benson & Gary M. Marsh (2017): Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology, Inhalation Toxicology, DOI: 10.1080/08958378.2017.1336187. Inhalation Toxicology, 29(9), 387–388. https://doi.org/10.1080/08958378.2017.1385662

Finkelstein, Murray M. Re: Mortality of Talc Miners and Millers From Val Chisone, Northern Italy, 59 J. Occup. Environ. Med. e194 (2017).

Finkelstein, M.M. 2018. Letter Concerning: Glynn ME, Keeton KA, Gaffney SH, Sahmel J. Ambient Asbestos Fiber Concentrations and Long-Term Trends in Pleural Mesothelioma Incidence Between Urban and Rural Areas in the United States (1973-2012). Risk Analysis 2018;38(3):454-471. Risk Anal. 38(8):1521-1523.

Finley, B. L., Pierce, J. S., Phelka, A. D., Adams, R. E., Paustenbach, D. J., Thuett, K. A., & Barlow, C. A. (2012). Evaluation of tremolite asbestos exposures associated with the use of commercial products. Critical Reviews in Toxicology, 42(2), 119–146. https://doi.org/10.3109/10408444.2011.636028

Finley, B. L., Benson, S. M., & Marsh, G. M. (2017). Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology. Inhalation Toxicology, 29(4), 179–185. https://doi.org/10.1080/08958378.2017.1336187

Finley, B.L. et al. 2018. Response to letters regarding "Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology". Inhal.Toxicol. 30(1):1-4.

Fitzgerald, S. et al. 2019. Asbestos in commercial indian talc. Am J Ind.Med. 62(5):385-392.

Fiume, M. M. et al. 2015. Safety Assessment of Talc as Used in Cosmetics. Int.J Toxicol 34(1 Suppl):66S-129S.

Fleming, J. S. et al. 2006. Incessant ovulation, inflammation and epithelial ovarian carcinogenesis: revisiting old hypotheses. Mol.Cell Endocrinol. 247(1-2):4-21.

Fletcher, Nicole M. et al., Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer, 102 Free Radical Biology and Medicine 122–132 (2017).

Fletcher, Nicole, Memaj, Ira & Saed, Ghassan, Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells., Reproductive Sciences (2018), http://journals.sagepub.com/doi/pdf/10.1177/1933719118759999 (last visited Aug 29, 2018).

Fletcher, N. M., I. Memaj, and G. M. Saied. 2018. Talcum powder enhances oxidative stress in ovarian cancer cells. Reproductive Sciences 25(Supplement 1):214A-215A.

Fletcher, N. M. and G. M. Saed. 2018. Talcum powder enhances cancer antigen 125 levels in ovarian cancer cells. ABSTACT

Fletcher, N.M. et al. 2019. Molecular Basis Supporting the Association of Talcum Powder Use With Increased Risk of Ovarian Cancer. Reprod.Sci 26(12):1603-1612.

Fordyce, T.A. et al. 2019. A 37-year Update on Mortality Patterns in an Expanded Cohort of Vermont Talc Miners and Millers. J Occup.Environ.Med. 61(11):916-923.

Frank, C. and L. Jorge. 2011. An uncommon hazard: Pulmonary talcosis as a result of recurrent aspiration of baby powder. Respiratory Medicine CME 4:109-111.

Frazier-Jessen, M. R., Mott, F. J., Witte, P. L., & Kovacs, E. J. (1996). Estrogen suppression of connective tissue deposition in a murine model of peritoneal adhesion formation. Journal of Immunology (Baltimore, Md.: 1950), 156(8), 3036–3042.

Fubini, B. and I. Fenoglio. 2007. Toxic potential of mineral dusts. Elements 3:407-414.

Gabriel, I.M. et al. 2019. Douching, Talc Use, and Risk for Ovarian Cancer and Conditions Related to Genital Tract Inflammation. Cancer Epidemiol.Biomarkers Prev. 28(11):1835-1844.

GAO. 1978. Lack of authority hampers attempts to increase cosmetic safety. United States General Accounting Office.

García-Ramallo, E., Marques, T., Prats, N., Beleta, J., Kunkel, S. L., & Godessart, N. (2002). Resident cell chemokine expression serves as the major mechanism for leukocyte recruitment during local inflammation. Journal of Immunology (Baltimore, Md.: 1950), 169(11), 6467–6473.

Gardner, D. L., Fink, D. J., and Hassler, C. R. 1981. Potential delivery of contraceptive agents to the female reproductive tract In: Controlled release of pesticides and pharmaceuticals. Danny H.Lewis, Southern Research Institute: Birmingham, AL, chapter 8.

Gates, M. A., Tworoger, S. S., Terry, K. L., Titus-Ernstoff, L., Rosner, B., De Vivo, I., … Hankinson, S. E. (2008). Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian

cancer. Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 17(9), 2436–2444. https://doi.org/10.1158/1055-9965.EPI-08-0399

Germani, D. et al. 1999. Cohort mortality study of women compensated for asbestosis in Italy. Am.J Ind.Med. 36(1):129-134.

Gersten, R.A. et al. 2010. Maillard reaction of ribose 5-phosphate generates superoxide and glycation products for bovine heart cytochrome c reduction. Carbohydr.Res. 345(17):2499-2506.

Gertig, D. M. et al. 2000. Prospective study of talc use and ovarian cancer. J Natl.Cancer Inst. 92(3):249-252.

Ghio, A. J., Kennedy, T. P., Whorton, A. R., Crumbliss, A. L., Hatch, G. E., & Hoidal, J. R. (1992). Role of surface complexed iron in oxidant generation and lung inflammation induced by silicates. The American Journal of Physiology, 263(5 Pt 1), L511-518.

Ghio, A.J. et al. 2001. Talc should not be used for pleurodesis in patients with nonmalignant pleural effusions. Am.J.Respir.Crit Care Med. 164(9):1741

Gilbert, C. R., Furman, B. R., Feller-Kopman, D. J., & Haouzi, P. (2018). Description of Particle Size, Distribution, and Behavior of Talc Preparations Commercially Available Within the United States. Journal of Bronchology & Interventional Pulmonology, 25(1), 25–30. https://doi.org/10.1097/LBR.0000000000000420

Gilbert, C.R. and P. Haouzi. 2019. Particle size, distribution, and behavior of talc preparations: within the United States and beyond. Curr.Opin.Pulm.Med. 25(4):374-379.

Gloyne, S. R. 1935. Two cases of squamous carcinoma of the lung occurring in asbestosis. Tubercle 17(1):5-10,N1-N2.

Gloyne, S. R. (1932). THE ASBESTOSIS BODY. The Lancet, 219(5678), 1351–1356. https://doi.org/10.1016/S0140-6736(01)19401-8

Glynn, M.E. et al. 2018. Ambient Asbestos Fiber Concentrations and Long-Term Trends in Pleural Mesothelioma Incidence between Urban and Rural Areas in the United States (1973-2012). Risk Anal. 38(3):454-471.

Godard, B. et al. 1998. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. Am.J Obstet.Gynecol. 179(2):403-410.

Gondal, M. A. et al. 2012. Detection of toxic metals (lead and chromium) in talcum powder using laser induced breakdown spectroscopy. Appl.Opt. 51(30):7395-7401.

Gonzalez, N. L., O'Brien, K. M., D'Aloisio, A. A., Sandler, D. P., & Weinberg, C. R. (2016). Douching, Talc Use, and Risk of Ovarian Cancer. Epidemiology (Cambridge, Mass.), 27(6), 797–802. https://doi.org/10.1097/EDE.0000000000000528

Goodman, Julie E. et al. 2020. A critical review of talc and ovarian cancer. Journal of Toxicology and Environmental Health, Part B, 23:5, 183-213

Gordon, R. E., Fitzgerald, S., & Millette, J. (2014). Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. International Journal of Occupational and Environmental Health, 20(4), 318–332. https://doi.org/10.1179/2049396714Y.0000000081

Gordon, R.E. 2015. Response to RE: Gordon R, Fitzgerald S, and Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup Environ Health. 2014;20(4):318-332. Int J Occup.Environ.Health 21(4):342-346.

Gossett, D.R. and M.G. Del Carmen. 2020. Use of Powder in the Genital Area and Ovarian Cancer Risk: Examining the Evidence. JAMA 323(1):29-31.

Graham, J. and R. Graham. 1967. Ovarian cancer and asbestos. Environ.Res. 1(2):115-128.

Graham, J. D. and M. E. Jenkins. 1952. Value of modified starch as a substitute for talc. Lancet 1(6708):590-591.

Grant, J. B., Davies, J. D., Jones, J. V., Espiner, H. J., & Eltringham, W. K. (1976). The immunogenicity of starch glove powder and talc. The British Journal of Surgery, 63(11), 864–866.

Graves, D. T., & Jiang, Y. (1995). Chemokines, a family of chemotactic cytokines. Critical Reviews in Oral Biology and Medicine: An Official Publication of the American Association of Oral Biologists, 6(2), 109–118.

Green, A. et al. 1997. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int.J Cancer 71(6):948-951.

Green, F. H. (2000). Pulmonary responses to inhaled poorly soluble particulate in the human. Inhalation Toxicology, 12(1–2), 59–95. https://doi.org/10.1080/08958370050164897

Greenburg, L. 1947. The dust hazard in tremolite talc mining. Yale J Biol.Med. 19(4):481-501.

Greene, M. H., Clark, J. W., & Blayney, D. W. (1984). The epidemiology of ovarian cancer. Seminars in Oncology, 11(3), 209–226.

Griffiths, K., Chandler, J. A., Henderson, W. J., & Joslin, C. A. (1973). Ovarian cancer: some new analytical approaches. Postgraduate Medical Journal, 49(568), 69–72.

Grivennikov, S. I., F. R. Greten, and M. Karin. 2010. Immunity, inflammation, and cancer. Cell 140(6):883-899.

Gross, A. J., & Berg, P. H. (1995). A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. Journal of Exposure Analysis and Environmental Epidemiology, 5(2), 181–195.

Halme, J. et al. 1984. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet.Gynecol. 64(2):151-154.

Hamilton, J. A., G. McCarthy, and G. Whitty. 2001. Inflammatory microcrystals induce murine macrophage survival and DNA synthesis. Arthritis Res. 3(4):242-246.

Hamilton, T. C. et al. 1984. Effects of talc on the rat ovary. Br.J Exp.Pathol. 65(1):101-106.

Harlow, B. L. and N. S. Weiss. 1989. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am.J Epidemiol. 130(2):390-394.

Harlow, B. L. et al. 1992. Perineal exposure to talc and ovarian cancer risk. Obstet.Gynecol. 80(1):19-26.

Harlow, B. L., & Hartge, P. A. (1995). A review of perineal talc exposure and risk of ovarian cancer. Regulatory Toxicology and Pharmacology: RTP, 21(2), 254–260. https://doi.org/10.1006/rtph.1995.1039

Harper and Saed, Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes, In Press.

Hartge, P. et al. 1983. Talc and ovarian cancer. JAMA 250(14):1844

Havelock, J. C., Rainey, W. E., & Carr, B. R. (2004). Ovarian granulosa cell lines. Molecular and Cellular Endocrinology, 228(1–2), 67–78. https://doi.org/10.1016/j.mce.2004.04.018

Hayashi, Y. (1992). Overview of genotoxic carcinogens and non-genotoxic carcinogens. Experimental and Toxicologic Pathology: Official Journal of the Gesellschaft Fur Toxikologische Pathologie, 44(8), 465–471. https://doi.org/10.1016/S0940-2993(11)80159-4

Health Assessment Document for Talc. | National Technical Reports Library - NTIS. (n.d.). Retrieved from https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB92239524.xhtml

Heller, D.S. et al., Asbestos exposure and ovarian fiber burden, 29 Am. J. Ind. Med. 435–439 (1996).

Heller, D. S. et al. 1996. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am.J Obstet.Gynecol. 174(5):1507-1510.

Henderson, W. J. et al. 1971. Talc and carcinoma of the ovary and cervix. J Obstet.Gynaecol.Br.Commonw. 78(3):266-272.

Henderson, W. J., T. C. Hamilton, and K. Griffiths. 1979. Talc in normal and malignant ovarian tissue. Lancet 1(8114):499

Henderson, W. J. et al. 1986. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ.Res. 40(2):247-250.

Hensten-Pettersen A and A Hulterstrom 1980. Assessment of in vitro cytotoxicity of four RTV-Silicone elastomers used for maxillo-facial prostheses, Acta Odontol Scand 38(3) pp163-167

Herbst, A. L. (1994). The epidemiology of ovarian carcinoma and the current status of tumor markers to detect disease. American Journal of Obstetrics and Gynecology, 170(4), 1099–1105; discussion 1105-1107.

Hernández, L. G., van Steeg, H., Luijten, M., & van Benthem, J. (2009a). Mechanisms of non-genotoxic carcinogens and importance of a weight of evidence approach. Mutation Research, 682(2–3), 94–109. https://doi.org/10.1016/j.mrrev.2009.07.002

Hernández, L. G., van Steeg, H., Luijten, M., & van Benthem, J. (2009b). Mechanisms of non-genotoxic carcinogens and importance of a weight of evidence approach. Mutation Research, 682(2–3), 94–109. https://doi.org/10.1016/j.mrrev.2009.07.002

Hildick-Smith, G. (1975). Talc--recent epidemiological studies. Inhaled Particles, 4 Pt 2, 655–665.

Hildick-Smith, G., & Taetzsch, R. L. (1977). Assessment of statistical significance of clinical data. The Journal of the Medical Society of New Jersey, 74(12), 1056–1057.

Hildick-Smith, G. (1977). Safety of consumer cosmetic talc products. Journal of Toxicology and Environmental Health, 2(5), 1221–1222. https://doi.org/10.1080/15287397709529520

Hildick-Smith, G. Y. 1976. The biology of talc. Br.J Ind.Med. 33(4):217-229.

Hill, A. B. 1965. The environment and disease: Association or causation? Proc.R.Soc.Med. 58:295-300.

Hillegass, J. M. et al. 2010. Utilization of gene profiling and proteomics to determine mineral pathogenicity in a human mesothelial cell line (LP9/TERT-1). J Toxicol.Environ.Health A 73(5):423-436.

Hogue, W. L., Jr. and F. S. Mallette. 1949. A study of workers exposed to talc and other dusting compounds in the rubber industry. J.Ind.Hyg.Toxicol. 31(6):359-364.

Houghton, S. C. et al. 2014. Perineal powder use and risk of ovarian cancer. J Natl.Cancer Inst. 106(9)

Hourihane, D. O. and W. T. McCaughey. 1966. Pathological aspects of asbestosis. Postgrad.Med.J 42(492):613-622.

Huang et al 2011 J Toxicol Environ health 14 pp 179-245

Huff, J., Jacobson, M. F., & Davis, D. L. (2008). The limits of two-year bioassay exposure regimens for identifying chemical carcinogens. Environmental Health Perspectives, 116(11), 1439–1442. https://doi.org/10.1289/ehp.10716

Hughes, W. T. and T. Kalmer. 1966. Massive talc aspiration. Successful treatment with dexamethasone. Amer J Dis Child 111:653-654.

Hume, Anne, The Biodurability of Chrysotile Asbestos, 77 American Mineralogist 1125–1128 (1992).

Huncharek, M., J. F. Geschwind, and B. Kupelnick. 2003. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: a meta-analysis of 11,933 subjects from sixteen observational studies. Anticancer Res. 23(2C):1955-1960.

Huncharek, M. et al. 2007. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: a meta-analysis of nine observational studies. Eur.J Cancer Prev. 16(5):422-429.

Huncharek, M. and J. Muscat. 2011. Perineal talc use and ovarian cancer risk: a case study of scientific standards in environmental epidemiology. Eur.J.Cancer Prev. 20(6):501-507.

Hussain, A., & Ahsan, F. (2005). The vagina as a route for systemic drug delivery. Journal of Controlled Release: Official Journal of the Controlled Release Society, 103(2), 301–313. https://doi.org/10.1016/j.jconrel.2004.11.034

International Agency for Research on Cancer (IARC). 1987. IARC Monographs on the evaluations of carcinogenic risks to humans. Overall evaluations of carcinogenicity: An updating of IARC Monographs Volumes 1 to 42. World Health Organization International Agency for Research on Cancer.

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica and Some Silicates." IARC, 1987.

International Agency for Research on Cancer (IARC), "Overall Evaluations of the Carcinogenic Risks to Humans", IARC Supplement No. 7 (1987).

International Agency for Research on Cancer (IARC). 2006. IARC Monographs on the evaluations of carcinogenic risks to humans. Preamble. World Health Organization International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2010. IARC Monographs on the evaluations of carcinogenic risks to humans. Carbon black, titanium dioxide and talc. World Health Organization International Agency for Research on Cancer.

International Agency for Research on Cancer (IARC). 2012. IARC Monographs on the evaluations of carcinogenic risks to humans. Arsenic, metals, fibres and dusts. A review of human carcinogens. World Health Organization International Agency for Research on Cancer.

ILSI Risk Science Institute. (2000). The relevance of the rat lung response to particle overload for human risk assessment: a workshop consensus report. Inhalation Toxicology, 12(1–2), 1–17. https://doi.org/10.1080/08958370050164833

Iturralde, M. and P. F. Venter. 1981. Hysterosalpingo-radionuclide scintigraphy (HERS). Semin.Nucl.Med. 11(4):301-314.

Jackson, E. M. 1995. Consumer products: Cosmetics and topical over-the-counter drug products In: Regulatory Toxicology . Christopher P.Chengelis, Joseph F.Holson, and Shayne C.Gad, Raven Press, Ltd.: New York, chapter 5.

Jacob, S.L. et al. 2018. Cosmetics and Cancer: Adverse Event Reports Submitted to the Food and Drug Administration. JNCI Cancer Spectr. 2(2):ky012

Jaques, W. E. and K. Benirschke. 1952. Pulmonary talcosis with involvement of the stomach and the heart; report of a case. AMA.Arch.Ind.Hyg.Occup.Med. 5(5):451-463.

Jasuja, S. et al. 2017. Cosmetic Talc-Related Pulmonary Granulomatosis. J.Investig.Med.High Impact.Case.Rep. 5(3):2324709617728527

Jaurand, M.C. 1991. Mechanisms of Fibre Genotoxicity. In: Mechanisms in Fibre Carcinogenisis. Brown, R. C., Plenum Press: New York.

Jaurand, M.C. 1997. Mechanisms of fiber-induced genotoxicity. Environ.Health Perspect. 105 Suppl 5:1073-1084.

Jayson, G. C., Kohn, E. C., Kitchener, H. C., & Ledermann, J. A. (2014). Ovarian cancer. Lancet, 384(9951), 1376–1388. https://doi.org/10.1016/S0140-6736(13)62146-7

Jenkins, M. Q. 1963. Poisoning of the month. Dusting powder inhalation. J S.C.Med.Assoc. 59:62

Jones, H. B., & Grendon, A. (1975). Environmental factors in the origin of cancer and estimation of the possible hazard to man. Food and Cosmetics Toxicology, 13(2), 251–268.

Jordan, S. J. et al. 2007. Risk factors for benign serous and mucinous epithelial ovarian tumors. Obstet.Gynecol. 109(3):647-654.

Jurinski, J. B., & Rimstidt, J. D. (2001). Biodurability of talc. American Mineralogist, 86(4), 392–399.

Kadanali, S. et al. 2001. Evaluation of active and passive transport mechanisms in genital tracts of IUD-bearing women with radionuclide hysterosalpingoscintigraphy. Contraception 63(1):41-45.

Kadry, T.M. et al. 2019. Critical review of the association between perineal use of talc powder and risk of ovarian cancer. Reprod.Toxicol. 90:88-101.

Kaiser, W. et al. 1982. [Unspecific tissue reactions caused by glove powder]. Fortschr.Med. 100(25):1213-1216.

Kamp, D. W., E. Shacter, and S. A. Weitzman. 2011. Chronic inflammation and cancer: the role of the mitochondria. Oncology (Williston.Park) 25(5):400-10, 413.

Kang, N., D. Griffin, and H. Ellis. 1992. The pathological effects of glove and condom dusting powders. J.Appl.Toxicol. 12(6):443-449.

Karageorgi, S., Gates, M. A., Hankinson, S. E., & De Vivo, I. (2010). Perineal use of talcum powder and endometrial cancer risk. Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 19(5), 1269–1275. https://doi.org/10.1158/1055-9965.EPI-09-1221

Kasper, C. S. and P. J. Chandler, Jr. 1995. Possible morbidity in women from talc on condoms. JAMA 273(11):846-847.

Katsnelson, B. A., & Mokronosova, K. A. (1979). Non-fibrous mineral dusts and malignant tumors: an epidemiological study of mortality. Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association, 21(1), 15–20.

Keal, E. E. 1960. Asbestosis and abdominal neoplasms. Lancet 2(7162):1211-1216.

Keeton, K.A. et al. 2018. Response to Letter to the Editor Regarding "Ambient Asbestos Fiber Concentrations and Long-Term Trends in Pleural Mesothelioma Incidence Between Urban and Rural Areas in the United States (1973-2012)" by Finkelstein. Risk Anal. 38(8):1524-1528.

Kennedy, D. 1978. The Food and Drug Administration and the backward motion toward the source. Public Health Rep. 93(6):607-615.

Kennedy, L., Harley, R. A., Sahn, S. A., & Strange, C. (1995). Talc slurry pleurodesis. Pleural fluid and histologic analysis. Chest, 107(6), 1707–1712.

Keskin, N., Teksen, Y. A., Ongun, E. G., Ozay, Y., & Saygili, H. (2009a). Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Archives of Gynecology and Obstetrics, 280(6), 925–931. https://doi.org/10.1007/s00404-009-1030-3

Keskin, N., Teksen, Y. A., Ongun, E. G., Ozay, Y., & Saygili, H. (2009b). Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Archives of Gynecology and Obstetrics, 280(6), 925–931. https://doi.org/10.1007/s00404-009-1030-3

Khan, S. G., Rizvi, R. Y., Hadi, S. M., & Rahman, Q. (1991). Influence of silicic acid on in vitro depurination of DNA. Bulletin of Environmental Contamination and Toxicology, 47(3), 342–349.

Kirkland, D., Aardema, M., Henderson, L., & Müller, L. (2005). Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens I. Sensitivity, specificity and relative predictivity. Mutation Research, 584(1–2), 1–256. https://doi.org/10.1016/j.mrgentox.2005.02.004

Kissler, S. et al. 2004. Uterine contractility and directed sperm transport assessed by hysterosalpingoscintigraphy (HSSG) and intrauterine pressure (IUP) measurement. Acta Obstet.Gynecol.Scand. 83(4):369-374.

Klaunig, J. E. 2013. Chemical Carcinogenesis In: Casarett and Doull's Toxicology, The Basic Science of Poisons, 8th edition. Klaassen, C. D., The McGraw-Hill Companies, Inc.: New York, NY, chapter 8.

Kleinfeld, M., J. Messite, and I. R. Tabershaw. 1955. Talc pneumoconiosis. AMA.Arch.Ind.Health 12(1):66-72.

Kleinfeld, M. et al. 1963. Talc pneumoconiosis: A report of six patients with postmortem findings. Arch.Environ.Health 7:101-115.

Kleinfeld, M. et al. 1964. Lung function in talc workers. Arch.Environ.Health 9:559-566.

Kleinfeld, M. et al. 1967. Mortality among talc miners and millers in New York State. Arch.Environ.Health 14(5):663-667.

Kleinfeld, M., J. Messite, and A. M. Langer. 1973. A study of workers exposed to asbestiform minerals in commercial talc manufacture. Environ.Res. 6(2):132-143.

Kleinfeld, M.J. 1970. Industrial pulmonary disease: clinical and experimental observations. Trans.N.Y.Acad.Sci. 32(1):107-126.

Kunz, G. et al. 1996. The dynamics of rapid sperm transport through the female genital tract: evidence from vaginal sonography of uterine peristalsis and hysterosalpingoscintigraphy. Hum.Reprod. 11(3):627-632.

Kunz, G. et al. 1997. The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. Adv.Exp.Med.Biol. 424:267-277.

Kunz, G., Beil, D., Deiniger, H., Einspanier, A., Mall, G., & Leyendecker, G. (1997a). The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. Advances in Experimental Medicine and Biology, 424, 267–277.

Kunz, G., Beil, D., Deiniger, H., Einspanier, A., Mall, G., & Leyendecker, G. (1997b). The uterine peristaltic pump. Normal and impeded sperm transport within the female genital tract. Advances in Experimental Medicine and Biology, 424, 267–277.

Kunz, G. and G. Leyendecker. 2002. Uterine peristaltic activity during the menstrual cycle: characterization, regulation, function and dysfunction. Reprod.Biomed.Online. 4 Suppl 3:5-9.

Kunz, G. et al. 2007. Oxytocin--a stimulator of directed sperm transport in humans. Reprod.Biomed.Online. 14(1):32-39.

Kupryjanczyk, J. 1989. Adenomatoid tumour of the ovary and uterus in the same patient. Zentralbl.Allg.Pathol. 135(5):437-444.

Kurta, M. L. et al. 2012. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. Cancer Epidemiol.Biomarkers Prev. 21(8):1282-1292.

Kwa, M. et al. 2017. Adverse Events Reported to the US Food and Drug Administration for Cosmetics and Personal Care Products. JAMA Intern.Med.

Kwong, J., Chan, F. L., Wong, K., Birrer, M. J., Archibald, K. M., Balkwill, F. R., … Mok, S. C. (2009). Inflammatory Cytokine Tumor Necrosis Factor α Confers Precancerous Phenotype in an Organoid Model of Normal Human Ovarian Surface Epithelial Cells. Neoplasia (New York, N.Y.), 11(6), 529–541.

La Vecchia, C. (2001). Epidemiology of ovarian cancer: a summary review. European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP), 10(2), 125–129.

LaDUE, J. S. (1941). BRONCHIOLITIS FIBROSA OBLITERANS: REPORT OF A CASE. Archives of Internal Medicine, 68(4), 663–673. https://doi.org/10.1001/archinte.1941.00200100002001

Landskron, G. et al. 2014. Chronic inflammation and cytokines in the tumor microenvironment. Journal of Immunology Research 2014:1-19.

Langseth, H. and K. Kjaerheim. 2004. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scand.J Work Environ.Health 30(5):356-361.

Langseth, H., Johansen, B. V., Nesland, J. M., & Kjaerheim, K. (2007). Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society, 17(1), 44–49. https://doi.org/10.1111/j.1525-1438.2006.00768.x

Langseth, H., Hankinson, S. E., Siemiatycki, J., & Weiderpass, E. (2008). Perineal use of talc and risk of ovarian cancer. Journal of Epidemiology and Community Health, 62(4), 358–360. https://doi.org/10.1136/jech.2006.047894

Lauchlan, Stuart, The Secondary Mullerian System Revisited, International Journal of Gynecological Pathology 13:73-79

Leak, L. V. 1980. Lymphatic removal of fluids and particles in the mammalian lung. Environ.Health Perspect. 35:55-75.

Lee, P., Sun, L., Lim, C. K., Aw, S. E., & Colt, H. G. (2010). Selective apoptosis of lung cancer cells with talc. European Respiratory Journal, 35(2), 450–452. https://doi.org/10.1183/09031936.00113109

Lee, R. and O.D. Van. 2015. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup.Environ.Health 21(4):337-341.

Lee, R., & Van Orden, D. (2015). RE: Gordon R, Fitzgerald S, and Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. Int J Occup Environ Health. 2014;20(4):318-332. International Journal of Occupational and Environmental Health, 2049396715Y0000000005. https://doi.org/10.1179/2049396715Y.0000000005

Lehman, T. A., Modali, R., Boukamp, P., Stanek, J., Bennett, W. P., Welsh, J. A., … Rogan, E. M. (1993). p53 mutations in human immortalized epithelial cell lines. Carcinogenesis, 14(5), 833–839.

Lewis, D. H. (Ed.). (1981). Controlled Release of Pesticides and Pharmaceuticals. Springer US. Retrieved from //www.springer.com/us/book/9781475707397

Light, R. W. (2000). Talc should not be used for pleurodesis. American Journal of Respiratory and Critical Care Medicine, 162(6), 2024–2026. https://doi.org/10.1164/ajrccm.162.6.pc09-00b

Lockey, James, Nonasbestos Fibrous Minerals, University of Utah Medical Center, 1981

Longo, D. L. and R. C. Young. 1979. Cosmetic talc and ovarian cancer. Lancet 2(8138):349-351.

Longo, D.L. & R. C. Young, Cosmetic talc and ovarian cancer, 2 Lancet 1011–1012 (1979).

Lord, G. H. (1978). The biological effects of talc in the experimental animal: a literature review. Food and Cosmetics Toxicology, 16(1), 51–57.

Lu, H., W. Ouyang, and C. Huang. 2006. Inflammation, a key event in cancer development. Mol.Cancer Res. 4(4):221-233.

Lynch, H et al. Systematic Review of the Association Between Talc and Female Reproductive Tract Cancers. Frontiers in Toxicology August 7, 2023.

Lynch, H et al. Systematic Review of the Association Between Talc and Female Reproductive Tract Cancers. Frontiers in Toxicology Supplemental Online Content.

Magnani, C. et al. 2008. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. Occup.Environ.Med. 65(3):164-170.

Mandarino, A. et al. 2020. The effect of talc particles on phagocytes in co-culture with ovarian cancer cells. Environ.Res 180:108676

Mann, B. and J. B. Deasy. 1954. Talc pneumoconiosis in the textile industry. Br.Med.J 2(4902):1460-1461.

Marsh, G.M. et al. 2019. Occupational exposures to cosmetic talc and risk of mesothelioma: an updated pooled cohort and statistical power analysis with consideration of latency period. Inhal.Toxicol. 31(6):213-223.

Mattenklott, M. 2007. Asbestos in talcum powders and soapstone - the present state (TRANSLATION). Gefahrstoffe Reinhaltung der Luft 67((7-8)):287-291.

McCalley, M. G. et al. 1985. Radionuclide hysterosalpingography for evaluation of fallopian tube patency. J Nucl.Med. 26(8):868-874.

McDonald, S.A. et al. 2019. Migration of Talc From the Perineum to Multiple Pelvic Organ Sites. Am J Clin Pathol. 152(5):590-607.

McLaughlin, A. I., E. Rogers, and K. C. Dunham. 1949. Talc pneumoconiosis. Br.J.Ind.Med. 6(3):184-194.

Meisler, J. G. (2000). Toward optimal health: the experts discuss ovarian cancer. Journal of Women's Health & Gender-Based Medicine, 9(7), 705–710. https://doi.org/10.1089/15246090050147600

Merewether, E. R. A. 1930. The occurrence of pulmonary fibrosis and other pulmonary affections in asbestos workers. The Journal of Industry Hygiene and Asbstract of the Literature 12:198-222, 239-257.

Merewether, E. R. A. and Price, C. W. 1930. Report on effects of asbestos dust on the lungs and dust suppression in the asbestos industry. His Majesty's Stationery Office.

Merliss, R. R. 1971. Talc-treated rice and Japanese stomach cancer. Science 173(4002):1141-1142.

Merritt, M. A. et al. 2008. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. Int.J Cancer 122(1):170-176.

Micha J et al. Talc Powder and Ovarian Cancer: What is the Evidence? Arch Gynecol Obstet 2022; 306:931-933.

Michaels, D. Doubt is their product. How industry's assault on science threatens your health. 2008. Oxford University Press, Inc.: New York, NY.

Michaels, D. 2020. The Triumph of Doubt: Dark Money and the Science of Deception. Oxford University Press: New York, NY.

Michaels, D. 2019. Reimagining Our System for Public Health Protection. Am J Public Health 109(7):975-976.

Migaki, G. and F. M. Garner. 1969. Talc-induced granulomas in swine. J Am.Vet.Med.Assoc 155(10):1595-1596.

Miller, A. et al. 1971. Talc pneumoconiosis. Significance of sublight microscopic mineral particles. Am.J Med. 50(3):395-402.

Miller, J. W. and R. R. Sayers. 1936. The physiological response of peritoneal tissue to certain industrial and pure mineral dusts. Public Health Reports 51(49):1677-1689.

Millman, N. 1947. Pneumonoeoniosis due to talc in the cosmetic industry. Occupational Medicine 4(4):391-394.

Mills, P. K. et al. 2004. Perineal talc exposure and epithelial ovarian cancer risk in the Central Valley of California. Int.J Cancer 112(3):458-464.

Mirabelli, D. (2017). Letter on: "Cosmetic talc as a risk factor for pleural mesothelioma: a weight of evidence evaluation of the epidemiology." Inhalation Toxicology, 29(8), 341. https://doi.org/10.1080/08958378.2017.1385114

Mirabelli, D. (2018). Letter on: "Mortality of Talc Miners and Millers From Val Chisone, Northern Italy." Journal of Occupational and Environmental Medicine, 60(1), e72. https://doi.org/10.1097/JOM.0000000000001212

Mofenson, H. C. et al. 1981. Baby powder--a hazard! Pediatrics 68(2):265-266.

Moline, J. et al. 2020. Mesothelioma Associated With the Use of Cosmetic Talc. J Occup.Environ.Med. 62(1):11-17.

Moller, P. et al. 2010. Role of oxidative damage in toxicity of particulates. Free Radic.Res. 44(1):1-46.

Møller, P., Jacobsen, N. R., Folkmann, J. K., Danielsen, P. H., Mikkelsen, L., Hemmingsen, J. G., … Loft, S. (2010). Role of oxidative damage in toxicity of particulates. Free Radical Research, 44(1), 1–46. https://doi.org/10.3109/10715760903300691

Moller, P. et al. 2013. Oxidatively damaged DNA in animals exposed to particles. Crit Rev Toxicol 43(2):96-118.

Molnar, J. J., G. Nathenson, and S. Edberg. 1962. Fatal aspiration of talcum powder by a child, Report of a case. N.Engl.J Med. 266:36-37.

Moon, M. C. et al. 2011. Risk Assessment of Baby Powder Exposure through Inhalation. Toxicol.Res 27(3):137-141.

Morabia, A. 2019. Fighting Independent Risk Assessment of Talc and Glyphosate: Whose Benefit Is It Anyway? Am J Public Health 109(7):955-956.

Moskowitz, R. L. (1970). Talc pneumoconiosis: a treated case. Chest, 58(1), 37–41.

Moss, M. H. 1969. Dangers from talcum powder. Pediatrics 43(6):1058

Mossman, B.T. et al. 2013. New insights into understanding the mechanisms, pathogenesis, and management of malignant mesotheliomas. Am J Pathol. 182(4):1065-1077.

Mossman, B.T. 2018. Mechanistic in vitro studies: What they have told us about carcinogenic properties of elongated mineral particles (EMPs). Toxicol.Appl Pharmacol. 361:62-67.

Mostafa, S. A., Bargeron, C. B., Flower, R. W., Rosenshein, N. B., Parmley, T. H., & Woodruff, J. D. (1985). Foreign body granulomas in normal ovaries. Obstetrics and Gynecology, 66(5), 701–702.

Muscat, J. and M. Huncharek. 2005. Talc and anti-MUC1 antibodies. Cancer Epidemiol.Biomarkers Prev. 14(11 Pt 1):2679

Muscat, J. E., & Wynder, E. L. (1997). Re: "Perineal powder exposure and the risk of ovarian cancer." American Journal of Epidemiology, 146(9), 786.

Muscat, J. E. and M. S. Huncharek. 2008. Perineal talc use and ovarian cancer: a critical review. Eur.J Cancer Prev. 17(2):139-146.

Nadler, D. L., & Zurbenko, I. G. (2014). Estimating Cancer Latency Times Using a Weibull Model, 8.

Nam, K. and D. R. Gracey. 1972. Pulmonary talcosis from cosmetic talcum powder. JAMA 221(5):492-493.

Narang, S. et al. 1977. Dissolution of silicic acid from dusts of kaolin, mica and talc and its relation to their hemolytic activity. -- an in vitro study. Exp.Pathol.(Jena) 13(6):346-349.

Narod, S. A. (2016). Talc and ovarian cancer. Gynecologic Oncology, 141(3), 410–412. https://doi.org/10.1016/j.ygyno.2016.04.011

Nasreen, N. et al., Talc-induced expression of C-C and C-X-C chemokines and intercellular adhesion molecule-1 in mesothelial cells, 158 Am. J. Respir. Crit. Care Med. 971–978 (1998).

Nasreen, N., Mohammed, K. A., Dowling, P. A., Ward, M. J., Galffy, G., & Antony, V. B. (2000). Talc induces apoptosis in human malignant mesothelioma cells in vitro. American Journal of Respiratory and Critical Care Medicine, 161(2 Pt 1), 595–600. https://doi.org/10.1164/ajrccm.161.2.9904123

National Research Council. Risk assessment in the Federal Government: Managing the process. 1983. National Academy Press: Washington, DC.

National Research Council. Reference manual on scientific evidence. 2011. 3rd edition, The National Academies Press: Washington, D.C.

National Toxicology Program (NTP). 1993. NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(Non-Asbestiform) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Natl.Toxicol.Program.Tech.Rep.Ser. 421:1-287.

National Toxicology Program (NTP). 2016. NTP Report on carcinogens, fourteenth edition. Asbestos (CAS No. 1332-21-4). National Toxicology Program, Department of Health and Human Services.

Natow, A. J. 1986. Talc: need we beware? Cutis 37(5):328-329.

Negus, R. P., Stamp, G. W., Relf, M. G., Burke, F., Malik, S. T., Bernasconi, S., … Balkwill, F. R. (1995). The detection and localization of monocyte chemoattractant protein-1 (MCP-1) in human ovarian cancer. Journal of Clinical Investigation, 95(5), 2391–2396.

Neill, A. S., Nagle, C. M., Spurdle, A. B., & Webb, P. M. (2012). Use of talcum powder and endometrial cancer risk. Cancer Causes & Control: CCC, 23(3), 513–519. https://doi.org/10.1007/s10552-011-9894-5

Ness R 2015. Does Talc Exposure Cause Ovarian Cancer? Int J Gynecol Cancer Vol 25 Suppl 1 pp51

Ness, R. B. and C. Cottreau. 1999. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl.Cancer Inst. 91(17):1459-1467.

Ness, R. B. et al. 2000. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology 11(2):111-117.

Neumann, H.G. 2009. Risk assessment of chemical carcinogens and thresholds. Crit Rev.Toxicol. 39(6):449-461.

Newhouse, M. L. et al. 1972. A study of the mortality of female asbestos workers. Br.J Ind.Med. 29(2):134-141.

Newhouse, M. L. (1979). Cosmetic talc and ovarian cancer. Lancet, 2(8141), 528.

Newhouse, M. L., G. Berry, and J. C. Wagner. 1985. Mortality of factory workers in east London 1933-80. Br.J Ind.Med. 42(1):4-11.

Nielsen, A. M., Olsen, J. H., Madsen, P. M., Francis, D., & Almind, M. (1994). Peritoneal mesotheliomas in Danish women: review of histopathologic slides and history of abdominal surgery. Acta Obstetricia Et Gynecologica Scandinavica, 73(7), 581–585.

NIOSH. 1980. Workplaces exposure to asbestos: Review and recommendations. U.S. Department of Health and Human Services.

Nitta, M., Katabuchi, H., Ohtake, H., Tashiro, H., Yamaizumi, M., & Okamura, H. (2001). Characterization and tumorigenicity of human ovarian surface epithelial cells immortalized by SV40 large T antigen. Gynecologic Oncology, 81(1), 10–17. https://doi.org/10.1006/gyno.2000.6084

Nohmi, T., Masumura, K., & Toyoda-Hokaiwado, N. (2017). Transgenic rat models for mutagenesis and carcinogenesis. Genes and Environment: The Official Journal of the Japanese Environmental Mutagen Society, 39, 11. https://doi.org/10.1186/s41021-016-0072-6

O'Brien, K.M. et al. 2019. Perineal Talc Use, Douching, and the Risk of Uterine Cancer. Epidemiology 30(6):845-852.

O'Brien et al. Association of powder use in the genital area with risk of ovarian cancer-supplementary online content.

O'Brien et al. Association of powder use in the genital area with risk of ovarian cancer; JAMA, 2020;323(1):49-59.

O'Brien et al. Genital powder use and risk of ovarian cancer: a pooled analysis – ASPO Abstracts.

O’Brien and colleagues. Genital Powder Use and Ovarian Cancer Letters to the Editor. JAMA May 26, 2020. Vol. 323, Number 20; 2095-2097.

Oberdörster, G. (2002). Toxicokinetics and effects of fibrous and nonfibrous particles. Inhalation Toxicology, 14(1), 29–56. https://doi.org/10.1080/089583701753338622

Oliver, T. 1927. Clinical Aspects of Pulmonary Asbestosis. Br.Med.J 2(3491):1026-1027.

Occupational Safety and Health Administration (OSHA). 2012. Guidance on data evaluation for weight of evidence determination: Application to the 2012 hazard communication standard. https://www.osha.gov/weightofevidence/woe_guidance.pdf

Ovrevik, J. et al. 2016. Triggering Mechanisms and Inflammatory Effects of Combustion Exhaust Particles with Implication for Carcinogenesis. Basic Clin.Pharmacol.Toxicol.

Ozesmi, M., Patiroglu, T. E., Hillerdal, G., & Ozesmi, C. (1985). Peritoneal mesothelioma and malignant lymphoma in mice caused by fibrous zeolite. British Journal of Industrial Medicine, 42(11), 746–749.

Paoletti, L. et al. 1984. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regul.Toxicol.Pharmacol. 4(3):222-235.

Parmley, T. H. and J. D. Woodruff. 1974. The ovarian mesothelioma. Am.J Obstet.Gynecol. 120(2):234-241.

Patro, M. et al. 2019. Blowing Balloons and Pulmonary Talcosis: An Uncommon Hazard. Indian J Occup.Environ.Med. 23(2):90-92.

Pelfrène, A., & Shubik, P. (1975). [Is talc a carcinogen? Review of current data]. La Nouvelle Presse Médicale, 4(11), 801–803.

Pelling, D. and J. G. Evans. 1986. Long-term peritoneal tissue response in rats to mould-release agents and lubricant powder used on surgeons' gloves. Food Chem.Toxicol 24(5):425-430.

Penninkilampi, R. and G. D. Eslick. 2018. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology 29(1):41-49.

Phillips, J. C. et al. 1978. Studies on the absorption and disposition of 3H-labelled talc in the rat, mouse, guinea-pig and rabbit. Food Cosmet.Toxicol 16(2):161-163.

Phung, M et al. Effects of Risk Factors for Ovarian Cancer in Women With and Without Endometriosis. Fertil and Steril 2022.

Phung, M et al. Effects of Risk Factors for Ovarian Cancer in Women With and Without Endometriosis. Supplemental Content Online.

Pierce, J. S., Riordan, A. S., Miller, E. W., Gaffney, S. H., & Hollins, D. M. (2017). Evaluation of the presence of asbestos in cosmetic talcum products. Inhalation Toxicology, 29(10), 443–456. https://doi.org/10.1080/08958378.2017.1392656

Pira, E., Coggiola, M., Ciocan, C., Romano, C., La Vecchia, C., Pelucchi, C., & Boffetta, P. (2017a). Mortality of Talc Miners and Millers From Val Chisone, Northern Italy: An Updated Cohort Study. Journal of Occupational and Environmental Medicine, 59(7), 659–664. https://doi.org/10.1097/JOM.0000000000000992

Pira, E., Coggiola, M., Ciocan, C., Romano, C., La Vecchia, C., Pelucchi, C., & Boffetta, P. (2017b). Response to Letter to the Editor On the Mortality of Talc Miners and Millers From Val Chisone, Northern Italy. Journal of Occupational and Environmental Medicine, 59(10), e195. https://doi.org/10.1097/JOM.0000000000001138

Pira, E., Coggiola, M., Ciocan, C., Romano, C., La Vecchia, C., Pelucchi, C., & Boffetta, P. (2018). Response to Letter to the Editor on the Mortality of Talc Miners and Millers From Val Chisone, Northern

Italy. Journal of Occupational and Environmental Medicine, 60(1), e73. https://doi.org/10.1097/JOM.0000000000001213

Plant, N. (2008). Can systems toxicology identify common biomarkers of non-genotoxic carcinogenesis? Toxicology, 254(3), 164–169. https://doi.org/10.1016/j.tox.2008.07.001

Pogribny, I. P. (2010). Epigenetic events in tumorigenesis: putting the pieces together. Experimental Oncology, 32(3), 132–136.

Pogribny, Igor P., & Rusyn, I. (2013). Environmental toxicants, epigenetics, and cancer. Advances in Experimental Medicine and Biology, 754, 215–232. https://doi.org/10.1007/978-1-4419-9967-2_11

Pooley, F. D. and N. Rowlands. 1975. Chemical and physical properties of British talc powders. Inhaled.Part 4 Pt 2:639-646.

Porro, F. W., J. R. Patton, and A. A. Hobbs Jr. 1942. Pneumoconiosis in the talc industry. The American Journal of Roentgenology 47(4):507-524.

Porro, F. W. and N. M. Levine. 1946. Pathology of talc pneumoconiosis with report of an autopsy. North N.Y.Med.J. 3:23-25.

Pott, F. and K. H. Friedrichs. 1972. [Tumors in the rat following intraperitoneal injections of fibrous dust]. Naturwissenschaften 59(7):318

Pott, F., F. Huth, and K. H. Friedrichs. 1974. Tumorigenic effect of fibrous dusts in experimental animals. Environ.Health Perspect. 9:313-315.

Price, B. (2010). Industrial-grade talc exposure and the risk of mesothelioma. Critical Reviews in Toxicology, 40(6), 513–530. https://doi.org/10.3109/10408441003646781

Purdie, D. et al. 1995. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int.J Cancer 62(6):678-684.

Qiao, Y., Yang, T., Gan, Y., Li, W., Wang, C., Gong, Y., & Lu, Z. (2018). Associations between aspirin use and the risk of cancers: a meta-analysis of observational studies. BMC Cancer, 18(1), 288. https://doi.org/10.1186/s12885-018-4156-5

Quignard, S. et al. 2017. Silica nanoparticles as sources of silicic acid favoring wound healing in vitro. Colloids Surf.B Biointerfaces. 155:530-537.

Radic, I. et al. 1988. Immunosuppression induced by talc granulomatosis in the rat. Clin Exp.Immunol. 73(2):316-321.

Rahman, Q., Alvi, N. K., Rizvi, R. Y., & Hadi, S. M. (1985). Interaction of DNA with Silicic Acid. In E. G. Beck & J. Bignon (Eds.), In Vitro Effects of Mineral Dusts: Third International Workshop (pp. 543–548). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-642-70630-1_72

Rakoff-Nahoum, S. 2006. Why cancer and inflammation? Yale J Biol Med. 79(3-4):123-130.

Rasmussen, P.E. et al. 2019. Characterization of Airborne Particles Emitted During Application of Cosmetic Talc Products. Int J Environ.Res Public Health 16(20)

Rehman, G. et al. 2013. Determination of toxic heavy metals in different brands of talcum powder. Int J Appl Nat Sci 2(2):45-52.

Reid, B. M., Permuth, J. B., & Sellers, T. A. (2017). Epidemiology of ovarian cancer: a review. Cancer Biology & Medicine, 14(1), 9–32. https://doi.org/10.20892/j.issn.2095-3941.2016.0084

Reverso-Meinietti, J., Vandenbos, F., Risso, K., Coyne, J., Leroy, S., Padovani, B., & Burel-Vandenbos, F. (2018). [Pulmonary intravascular talcosis: A case report]. La Revue De Medecine Interne, 39(8), 658–660. https://doi.org/10.1016/j.revmed.2018.03.017

Roberts, G. B. 1947. Granuloma of the fallopian tube due to surgical glove talc; silicious granuloma. Br.J.Surg. 34(136):417-423.

Roden, A. C., & Camus, P. (2018). Iatrogenic pulmonary lesions. Seminars in Diagnostic Pathology, 35(4), 260–271. https://doi.org/10.1053/j.semdp.2018.03.002

Rodenberg, H. 2019. Reliance, Not Responsibility: Relations Between Science and Industry. Am J Public Health 109(7):980-981.

Roe, F. J. (1979). Controversy: cosmetic talc and ovarian cancer. Lancet, 2(8145), 744.

Rohl, A. N. and A. M. Langer. 1974. Identification and quantitation of asbestos in talc. Environ.Health Perspect. 9:95-109.

Rohl, A. N. et al. 1976. Consumer talcums and powders: mineral and chemical characterization. J Toxicol Environ.Health 2(2):255-284.

Rosenblatt, K. A., M. Szklo, and N. B. Rosenshein. 1992. Mineral fiber exposure and the development of ovarian cancer. Gynecol.Oncol. 45(1):20-25.

Rosenblatt, K. A., Mathews, W. A., Daling, J. R., Voigt, L. F., & Malone, K. (1998). Characteristics of women who use perineal powders. Obstetrics and Gynecology, 92(5), 753–756.

Rosenblatt, K. A. et al. 2011. Genital powder exposure and the risk of epithelial ovarian cancer. Cancer Causes Control 22(5):737-742.

Rosenkranz, H. S. (1996). Mutagenic nitroarenes, diesel emissions, particulate-induced mutations and cancer: an essay on cancer-causation by a moving target. Mutation Research, 367(2), 65–72.

Rosner, D. et al. 2019. "Nondetected": The Politics of Measurement of Asbestos in Talc, 1971-1976. Am J Public Health 109(7):969-974.

Rosner, D. et al. 2020. "Baby Powders and the Precautionary Principle" AJPH, September 2020, Vol 110, No. 9

Ross, M. (1974). Geology, asbestos, and health. Environmental Health Perspectives, 9, 123–124.

Rothman, K. J. and Greenland, S. 1998. Causation and causal inference In: Modern Epidemiology, 2nd Edition edition. KJ Rothman and S Greenland, Lippincott Williams & Wilkins: Philadelphia, chapter 2.

Rothman, K. J., Greenland, S., & Lash, T. L. (2008). Modern Epidemiology. Lippincott Williams & Wilkins.

Rubino, G. F. et al. 1976. Mortality study of talc miners and millers. J.Occup.Med. 18(3):187-193.

Saed, G. M., M. P. Diamond, and N. M. Fletcher. 2017. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. Gynecol.Oncol. 145(3):595-602.

Saed, G.M., R.T. Morris and N. M. Fletcher (March 28th 2018). New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress, Ovarian Cancer, Omer Devaja and Andreas Papadopoulos, IntechOpen, DOI: 10.5772/intechopen.73860. Available from: https://www.intechopen.com/books/ovarian-cancer-from-pathogenesis-to-treatment/new-insights-into-the-pathogenesis-of-ovarian-cancer-oxidative-stress

Sagae, S., Mori, M., & Moore, M. A. (2002). Risk Factors for Ovarian Cancers: Do Subtypes Require Separate Treatment in Epidemiological Studies? Asian Pacific Journal of Cancer Prevention: APJCP, 3(1), 5–16.

Sahn, S. A. (2000). Talc should be used for pleurodesis. American Journal of Respiratory and Critical Care Medicine, 162(6), 2023–2024; discussion 2026. https://doi.org/10.1164/ajrccm.162.6.pc09-00a

Salehi, F., Dunfield, L., Phillips, K. P., Krewski, D., & Vanderhyden, B. C. (2008). Risk Factors for Ovarian Cancer: An Overview with Emphasis on Hormonal Factors. Journal of Toxicology and Environmental Health, Part B, 11(3–4), 301–321. https://doi.org/10.1080/10937400701876095

Samet, J.M. 2019. Expert Review Under Attack: Glyphosate, Talc, and Cancer. Am J Public Health 109(7):976-978.

Sasaki, Y. F., Sekihashi, K., Izumiyama, F., Nishidate, E., Saga, A., Ishida, K., & Tsuda, S. (2000). The comet assay with multiple mouse organs: comparison of comet assay results and carcinogenicity with 208 chemicals selected from the IARC monographs and U.S. NTP Carcinogenicity Database. Critical Reviews in Toxicology, 30(6), 629–799. https://doi.org/10.1080/10408440008951123

Savant, S., Shruthi Sriramkumar and Heather M. O'Hagan. "The Role of Inflammation and Inflammatory Mediators in the Development, Progression, Metastasis, and Chemoresistance of Epithelial Ovarian Cancer."

Sax, N. I. Dangerous properties of industrial materials. A completely revised and enlarged edition of Handbook of Dangerous Materials. 1957. Reinhold Publishing Corporation: New York.

Saxen, A. and P. I. Tuovinen. 1947. Experimental and clinical observations on granulomas caused by talc and some other substances. Acta Chir Scand. 96(2):131-151.

Saxen, L. et al. 1963. Peritoneal foreign-body reaction caused by condom emulsion. Lancet 1(7294):1295-1296.

Schepers, G. W. and T. M. Durkan. 1955. The effects of inhaled talc-mining dust on the human lung. AMA.Arch.Ind.Health 12(2):182-197.

Schildkraut, J. M. et al. 2016. Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). Cancer Epidemiol.Biomarkers Prev. 25(10):1411-1417.

Schulz, R. Z. and C. R. Williiams. 1942. Commercial talc: Animal and mineralogical studies. Journal of Industrial Hygiene and Toxicology 24(4):75-79.

Seeler, A., J. S. Gryboski, and H. E. MacMahon. 1959. Talc pneumoconiosis. AMA.Arch.Ind.Health 19(4):392-402.

Seeler, Albert O. Toxic Hazards: Talc Pneumoconiosis, 261 New England Journal of Medicine 1084–1085 (1959).

Seiler, H. E. 1928. A case of pneumoconiosis: Result of the inhalation of asbestos dust. Br.Med.J 2(3543):982-980.

Selikoff, I. J., J. Churg, and E. C. Hammond. 1964. Asbestos exposure and neoplasia. JAMA 188:22-26.

Senthil, K., S. Aranganathan, and N. Nalini. 2004. Evidence of oxidative stress in the circulation of ovarian cancer patients. Clin Chim.Acta 339(1-2):27-32.

Shan, Weiwei, and Jinsong Liu. "Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer." Cell Cycle 8, no. 19 (2009): 3107–11. https://doi.org/10.4161/cc.8.19.9590.

Shattock, S. G. (1916). The Traumatic Causation of Appendicitis. Proceedings of the Royal Society of Medicine, 9(Pathol Sect), 23–88.

Shen, N., Weiderpass, E., Antilla, A., Goldberg, M. S., Vasama-Neuvonen, K. M., Boffetta, P., … Partanen, T. J. (1998). Epidemiology of occupational and environmental risk factors related to ovarian cancer. Scandinavian Journal of Work, Environment & Health, 24(3), 175–182.

Shim, I. et al. 2015. Inhalation of Talc Induces Infiltration of Macrophages and Upregulation of Manganese Superoxide Dismutase in Rats. Int.J Toxicol. 34(6):491-499.

Shoham, Z. (1994). Epidemiology, etiology, and fertility drugs in ovarian epithelial carcinoma: where are we today? Fertility and Sterility, 62(3), 433–448.

Shukla, A. et al. 2009. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. Am.J.Respir.Cell Mol.Biol. 41(1):114-123.

Shushan, A. et al. 1996. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. Fertil.Steril. 65(1):13-18.

Sjosten, A. C., H. Ellis, and G. A. Edelstam. 2004. Retrograde migration of glove powder in the human female genital tract. Hum.Reprod. 19(4):991-995.

Slomovitz B, et al. Oct. 21, 2020. Asbestos and ovarian cancer: examining the historical evidence Int J Gynecol Cancer 2020;0:1–7. doi:10.1136/ijgc-2020-001672

Solleveld, H. A., Haseman, J. K., & McConnell, E. E. (1984). Natural history of body weight gain, survival, and neoplasia in the F344 rat. Journal of the National Cancer Institute, 72(4), 929–940.

Stanley, H. D., & Norwood, R. E. (1976). The Detection and Identification of Asbestos and Asbestiform Minerals in Talc. Retrieved from http://tobaccodocuments.org/pm/2063105118-5131.html

Stannard, L., Doak, S. H., Doherty, A., & Jenkins, G. J. (2017). Is Nickel Chloride really a Non-Genotoxic Carcinogen? Basic & Clinical Pharmacology & Toxicology, 121 Suppl 3, 10–15. https://doi.org/10.1111/bcpt.12689

Stanton, M. F. et al. 1981. Relation of particle dimension to carcinogenicity in amphibole asbestoses and other fibrous minerals. J Natl.Cancer Inst. 67(5):965-975.

Steiling, W., Almeida, J. F., Assaf Vandecasteele, H., Gilpin, S., Kawamoto, T., O'Keeffe, L., … Bowden, A. M. (2018). Principles for the safety evaluation of cosmetic powders. Toxicology Letters. https://doi.org/10.1016/j.toxlet.2018.08.011

Stenback, F. and J. Rowlands. 1978. Role of talc and benzo(a)pyrene in respiratory tumor formation. An experimental study. Scand.J Respir.Dis. 59(3):130-140.

Stenback, F., Wasenius, V.-M., and Rowland, J. 1986. Alveolar and interstitial changes in silicate-associated lung tumors in Syrian hamsters. In: Silica, silicosis, and cancer: controversy in occupational medicine, Vol. 2 edition, chapter 21.

Straif, Kurt Update of the scientific evidence on asbestos and cancer (2011).

Stuart, B. O. 1984. Deposition and clearance of inhaled particles. Environ.Health Perspect. 55:369-390.

Styles, J. A., & Wilson, J. (1973). Comparison between in vitro toxicity of polymer and mineral dusts and their fibrogenicity. The Annals of Occupational Hygiene, 16(3), 241–250.

Sueblinvong, T., & Carney, M. E. (2009). Ovarian cancer: risks. Hawaii Medical Journal, 68(2), 40–46.

Suzuki, Y. and N. Kohyama. 1991. Translocation of inhaled asbestos fibers from the lung to other tissues. Am.J Ind.Med. 19(6):701-704.

Tarchi, M. et al. 1994. Cohort mortality study of rock salt workers in Italy. Am.J Ind.Med. 25(2):251-256.

Terry, K. L. et al. 2013. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev.Res.(Phila) 6(8):811-821.

Thomas, C. A., & Seelig, M. G. (1952). US2621333A. United States. Retrieved from https://patents.google.com/patent/US2621333/en

Tilkes, F., & Beck, E. G. (1983). Macrophage functions after exposure to mineral fibers. Environmental Health Perspectives, 51, 67–72.

Tortolero-Luna, G., & Mitchell, M. F. (1995). The epidemiology of ovarian cancer. Journal of Cellular Biochemistry. Supplement, 23, 200–207.

Trabert, B. et al. 2014. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the prostate, lung, colorectal and ovarian cancer (PLCO) screening trial. Gynecol.Oncol. 135(2):297-304.

Trautwein, G. and C. F. Helmboldt. 1967. Experimental pulmonary talcum granuloma and epithelial hyperplasia in the chinchilla. Pathol.Vet. 4(3):254-267.

Turk, J. L., & Narayanan, R. B. (1981). The monocyte-macrophage system in granulomatous inflammation. Haematology and Blood Transfusion, 27, 101–107.

Tye, M. J., Hashimoto, K., & Fox, F. (1966). Talc granulomas of the skin. JAMA, 198(13), 1370–1372.

Tzonou, A. et al. 1993. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int.J Cancer 55(3):408-410.

Urban, Nicole et al., Identifying post-menopausal women at elevated risk for epithelial ovarian cancer, 139 Gynecologic Oncology 253–260 (2015).

U.S. Environmental Protection Agency (USEPA), 1983. Risk assessment in the federal government: Managing the process. National Research Council on the Institutional Means for Assessment of Risks to Public Health, Commission on Life Sciences, http://www.epa.gov/region9/science/seminars/2012/red-book.pdf (last visited Jan 22, 2015).

U.S. Environmental Protection Agency (USEPA), "Methodology for the Measurement of Airborne Asbestos by Electron Microscopy", July 1984.

United States Environmental Protection Agency (USEPA). 1986. Guidelines for mutagenicity risk assessment. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23160&CFID=65932199&CFTOKEN=24176705

United States Environmental Protection Agency (USEPA). 1986. Health effects assessment for asbestos.

United States Environmental Protection Agency (USEPA). 1992. Health assessment document for talc. Office of Research and Development.

United States Environmental Protection Agency (USEPA). 1994. Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=71993&CFID=65932266&CFTOKEN=97071893

United States Environmental Protection Agency (USEPA). 1996. Ambient Levels and Noncancer Health Effects of Inhaled Crystalline and Amorphous Silica. Office of Research and Development.

United States Environmental Protection Agency (USEPA). 2000. Supplementary guidance for conducting health risk assessment of chemical mixtures. USEPA Risk Assessment Forum.

United States Environmental Protection Agency (USEPA). 2014. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. https://www.epa.gov/risk/methods-derivation-inhalation-reference-concentrations-and-application-inhalation-dosimetry (last visited Aug 29, 2018).

United States Environmental Protection Agency (USEPA). 2015. EDSP: Weight of evidence analysis of potential interaction with the estrogen, androgen or tyroid pathways. Chemical: Acephate.

https://www.epa.gov/sites/production/files/2015-06/documents/acephate-103301_2015-06-29_txr0057153.pdf

United States Food and Drug Administration (USFDA). 1997. Guidance for industry: S1B testing for carcinogenicity of pharmaceuticals. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf

USFDA. 1997. Guidance for industry: S1B testing for carcinogenicity of pharmaceuticals. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm074916.pdf

United States Food and Drug Administration (USFDA). 2006. Guidance for industry and review staff: Recommended approaches to integration of genetic toxicology study results. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079257.pdf

United States Food and Drug Administration (USFDA). 2011. Guidance for industry: Reproductive and developmental toxicities - integrating study resulats to assess concerns. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079240.pdf

United States Food and Drug Administration (USFDA). 2014. Talc. http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm

United States Food and Drug Administration (USFDA). 2016. How FDA evaluates regulated products: Cosmetics. http://www.fda.gov/aboutfda/transparency/basics/ucm262353.htm

United States Food and Drug Administration (USFDA). 2016. FDA authority over cosmetics: How cosmetics are not FDA-approved, but are FDA-regulated. http://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074162.htm

United States Food and Drug Administration (USFDA). 2016. Food and Drug Administration: Cosmetic labeling guide. http://www.fda.gov/downloads/Cosmetics/Labeling/UCM391202.pdf

United States Food and Drug Administration (USFDA). 2016. Draft guidance for industry: Cosmetic Good Manufacturing Practices. http://www.fda.gov/cosmetics/guidanceregulation/guidancedocuments/ucm353046.htm

United States Food and Drug Administration (USFDA). November 2023. Guidance for Industry: Compliance Policy for Cosmetic Product Facility Registration and Cosmetic Product Listing. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-compliance-policy-cosmetic-product-facility-registration-and-cosmetic-product

United States Geological Survey (USGS). 2001. Some facts about asbestos. U.S. Department of the Interior.

Vallyathan, N. V., & Craighead, J. E. (1981). Pulmonary pathology in workers exposed to nonasbestiform talc. Human Pathology, 12(1), 28–35.

Vallyathan, V. et al. 1992. Enhanced generation of free radicals from phagocytes induced by mineral dusts. Am.J.Respir.Cell Mol.Biol. 6(4):404-413.

Van Gosen, B. S., Lowers, H. A., Sutley, S. J., & Gent, C. A. (2004). Using the geologic setting of talc deposits as an indicator of amphibole asbestos content. Environmental Geology, 45(7), 20. https://doi.org/10.1007/s00254-003-0955-2

van Huisstede, A. et al. 2010. Talcosis due to abundant use of cosmetic talcum powder. Eur.Respir.Rev. 19(116):165-168.

Vannucci, J., Bellezza, G., Matricardi, A., Moretti, G., Bufalari, A., Cagini, L., … Daddi, N. (2018). Observational analysis on inflammatory reaction to talc pleurodesis: Small and large animal model series review. Experimental and Therapeutic Medicine, 15(1), 733–738. https://doi.org/10.3892/etm.2017.5454

Venter, P. F. and M. Iturralde. 1979. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. S.Afr.Med.J 55(23):917-919.

Vineis, P. 2019. Public Health and Independent Risk Assessment. Am J Public Health 109(7):978-980.

Wagner, J. C. et al. 1975. Animal experiments with talc. Inhaled.Part 4 Pt 2:647-654.

Wang, X. et al. 2013. Cause-specific mortality in a Chinese chrysotile textile worker cohort. Cancer Sci 104(2):245-249.

Wang, Y., Ma, J., Shen, H., Wang, C., Sun, Y., Howell, S. B., & Lin, X. (2014). Reactive oxygen species promote ovarian cancer progression via the HIF-1α/LOX/E-cadherin pathway. Oncology Reports, 32(5), 2150–2158. https://doi.org/10.3892/or.2014.3448

Warheit, D. B., Kreiling, R., & Levy, L. S. (2016). Relevance of the rat lung tumor response to particle overload for human risk assessment-Update and interpretation of new data since ILSI 2000. Toxicology, 374, 42–59. https://doi.org/10.1016/j.tox.2016.11.013

Wehner, A. P., Tanner, T. M., & Buschbom, R. L. (1977). Absorption of ingested talc by hamsters. Food and Cosmetics Toxicology, 15(5), 453–455.

Wehner, A. P., Zwicker, G. M., & Cannon, W. C. (1977). Inhalation of talc baby powder by hamsters. Food and Cosmetics Toxicology, 15(2), 121–129.

Wehner, A. P., Wilkerson, C. L., Cannon, W. C., Buschbom, R. L., & Tanner, T. M. (1977). Pulmonary deposition, translocation and clearance of inhaled neutron-activated talc in hamsters. Food and Cosmetics Toxicology, 15(3), 213–224.

Wehner, A. P., Stuart, B. O., & Sanders, C. L. (1979). Inhalation studies with Syrian golden hamsters. Progress in Experimental Tumor Research, 24, 177–198.

Wehner, A. P. (1980). Effects of inhaled asbestos, asbestos plus cigarette smoke, asbestos-cement and talc baby powder in hamsters. IARC Scientific Publications, (30), 373–376.

Wehner, A. P. et al. 1985. Do particles translocate from the vagina to the oviducts and beyond? Food Chem.Toxicol. 23(3):367-372.

Wehner, A. P., R. E. Weller, and E. A. Lepel. 1986. On talc translocation from the vagina to the oviducts and beyond. Food Chem.Toxicol. 24(4):329-338.

Wehner, A. P. (1994). Biological effects of cosmetic talc. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association, 32(12), 1173–1184.

Wehner, Alfred P. Cosmetic talc should not be listed as a carcinogen: comments on NTP's deliberations to list talc as a carcinogen, 36 Regul. Toxicol. Pharmacol. 40–50 (2002).

Wells, I. P., P. A. Dubbins, and W. F. Whimster. 1979. Pulmonary disease caused by the inhalation of cosmetic talcum powder. Br.J Radiol. 52(619):586-588.

Wentzensen, N and O'Brien, K. Talc, Body Powder, and Ovarian Cancer: A summary of the Epidemiologic Evidence. Gynecologic Oncology July 2021. https://doi.org/10.1016/j.ygyno.2021.07.032

Wentzensen, N., & Wacholder, S. (2014). Talc Use and Ovarian Cancer: Epidemiology Between a Rock and a Hard Place. Journal of the National Cancer Institute, 106(9), dju260. https://doi.org/10.1093/jnci/dju260

Wentzensen, N. et al. 2016. Ovarian Cancer Risk Factors by Histologic Sybtype: An Analysis From the Ovarian Cancer Cohort Consortium. Journal of Clincical Oncology Vol 34, No. 24

Werebe, E.C. et al. 1999. Systemic distribution of talc after intrapleural administration in rats. Chest 115(1):190-193.

Wergeland, E., Gjertsen, F., Vos, L., & Grimsrud, T. K. (2017). Cause-specific mortality and cancer morbidity in 390 male workers exposed to high purity talc, a six-decade follow-up. American Journal of Industrial Medicine, 60(9), 821–830. https://doi.org/10.1002/ajim.22749

Whittemore, A. S. et al. 1988. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am.J Epidemiol. 128(6):1228-1240.

World Health Organization (WHO). 2000. Crystalline silica, quartz. World Health Organization.

World Health Organization (WHO) 2011. Update of the scientific evidence on asbestos and cancer. http://www.who.int/phe/news/events/international_conference/Session2_DrStraif.pdf

Whysner, J. and M. Mohan. 2000. Perineal application of talc and cornstarch powders: evaluation of ovarian cancer risk. Am.J Obstet.Gynecol. 182(3):720-724.

Wignall, B. K. and A. J. Fox. 1982. Mortality of female gas mask assemblers. Br.J Ind.Med. 39(1):34-38.

Williams, K. A., Labidi-Galy, S. I., Terry, K. L., Vitonis, A. F., Welch, W. R., Goodman, A., & Cramer, D. W. (2014). Prognostic significance and predictors of the neutrophil-to-lymphocyte ratio in ovarian cancer. Gynecologic Oncology, 132(3), 542–550. https://doi.org/10.1016/j.ygyno.2014.01.026

Wong, C. et al. 1999. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. Obstet.Gynecol. 93(3):372-376.

Wood, C. E., Hukkanen, R. R., Sura, R., Jacobson-Kram, D., Nolte, T., Odin, M., & Cohen, S. M. (2015). Scientific and Regulatory Policy Committee (SRPC) Review: Interpretation and Use of Cell Proliferation Data in Cancer Risk Assessment. Toxicologic Pathology, 43(6), 760–775. https://doi.org/10.1177/0192623315576005

Wood, W. B. 1929. Pulmonary asbestosis. Tubercle :23,353-363.

Woodworth, C. D., Mossman, B. T., & Craighead, J. E. (1982). Comparative effects of fibrous and nonfibrous minerals on cells and liposomes. Environmental Research, 27(1), 190–205.

Woolen S, Lazar, A and Smith-Bindman, R. Association Between the Frequent Use of Perineal Talcum Powder products and Ovarian Cancer: A Systematic Review and Meta-Analysis. J Gen Intern Med 2022.

Woolen S, Lazar, A and Smith-Bindman, R. Association Between the Frequent Use of Perineal Talcum Powder products and Ovarian Cancer. Supplemental Content Online.

Wright, H. R. et al. 1996. Potential toxicity of retrograde uterine passage of particulate matter. J Long.Term.Eff.Med.Implants. 6(3-4):199-206.

Wright, MD., Jason D., What Is New in Ovarian Cancer? Best Articles from the Past Year, Obstet Gynecol 2018; 132: 1498-9

Wu, A. H. et al. 2009. Markers of inflammation and risk of ovarian cancer in Los Angeles County. Int.J Cancer 124(6):1409-1415.

Wu, A.H. et al. 2015. African Americans and Hispanics remain at lower risk of ovarian cancer then Non-Hispanic Whites after considering non-genetic risk factors and oophorectomy rates. Cancer Epidemiol. Biomark. Prevent. 24:1094-1100.

Wyers, H. Asbestosis, 25 Postgrad Med J 631–638, illust (1949).

Wylie, A. G., Skinner, H. C., Marsh, J., Snyder, H., Garzione, C., Hodkinson, D., … Mossman, B. T. (1997). Mineralogical features associated with cytotoxic and proliferative effects of fibrous talc and asbestos on rodent tracheal epithelial and pleural mesothelial cells. Toxicology and Applied Pharmacology, 147(1), 143–150. https://doi.org/10.1006/taap.1997.8276

Yokoe, N., Katsuda, E., Kosaka, K., Hamanaka, R., Matsubara, A., Nishimura, M., … Kubo, A. (2017). Interstitial Lung Disease after Pleurodesis for Malignant Pleural Effusion. Internal Medicine (Tokyo, Japan), 56(14), 1791–1797. https://doi.org/10.2169/internalmedicine.56.7464

Yu, C., Tang, H., Guo, Y., Bian, Z., Yang, L., Chen, Y., … China Kadoorie Biobank Collaborative Group. (2018). Hot Tea Consumption and Its Interactions With Alcohol and Tobacco Use on the Risk for Esophageal Cancer: A Population-Based Cohort Study. Annals of Internal Medicine, 168(7), 489–497. https://doi.org/10.7326/M17-2000

Yumrutas, O., Kara, M., Atilgan, R., Kavak, S. B., Bozgeyik, I., & Sapmaz, E. (2015). Application of talcum powder, trichloroacetic acid and silver nitrate in female rats for non-surgical sterilization: evaluation of the apoptotic pathway mRNA and miRNA genes. International Journal of Experimental Pathology. https://doi.org/10.1111/iep.12123

Zazenski, R. et al. 1995. Talc: occurrence, characterization, and consumer applications. Regul.Toxicol.Pharmacol. 21(2):218-229.

Zervomanolakis, I. et al. 2007. Physiology of upward transport in the human female genital tract. Ann.N.Y.Acad.Sci. 1101:1-20.

APPENDIX D

Chemicals in the Johnson & Johnson Body Powder Fragrance with Irritant Properties

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
(d)-Limonene	Y		https://pubchem.ncbi.nlm.nih.gov/compound/440917#section=Safety-and-Hazards *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (96.26%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard SYMPTOMS: Symptoms of exposure to this compound may include irritation and sensitization of the skin. It may also cause eye irritation and damage. The substance *is irritating to the skin* and is mildly irritating to the eyes. IPCS, CEC; International Chemical Safety Card on d-Limonene. (April 2005). Available from, as of February 3, 2006: http://www.inchem.org/documents/icsc/icsc/eics0918.htm from HSDB https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+4186 HUMAN EXPOSURE AND TOXICITY: Skin irritation or sensitizing potential was reported following widespread use of this agent in various consumer products. *In humans, oxidation products or metabolites of d-limonene were shown to act as skin irritants. The potential occurrence of skin irritation necessitates regulation of this chemical as an ingredient in cosmetics.* http://www.thegoodscentscompany.com/data/rw1013772.html#tosafty European information : Most important hazard(s): *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitization by skin contact.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317* https://www.ewg.org/guides/substances/151421-dLimonene#.W37iluhKiUk Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/limonene-0 The safety of Limonene has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Limonene in fragrances because of potential sensitization. In Europe, Limonene is included on the list of "allergenic" substances. The European Cosmetics Directive requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Limonene must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin
1-(2,6,6-Trimethylcyclohex-2-en-1-yl)pent-1-en-3-one	Y		https://pubchem.ncbi.nlm.nih.gov/compound/5375218#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (17.53%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (81.57%): May cause an allergic skin reaction [Warning Sensitization, Skin]*

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			http://www.thegoodscentscompany.com/data/rw1032741.html#tosafty European information : Most important hazard(s): *R 36/37/38 - Irritating to eyes, respiratory system, and skin.*
1,2-Dimethoxy-4-prop-1-en-1-ylbenzene	Y		http://www.thegoodscentscompany.com/data/rw1011132.html#tosafty European information : Most important hazard(s): S 24/25 - Avoid contact with skin and eyes. https://chem.nlm.nih.gov/chemidplus/rn/93-16-3 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/cis-Methylisoeugenol#section=Hazards-Identification Signal: Warning GHS Hazard Statements *H317 (86.67%): May cause an allergic skin reaction [Warning Sensitization, Skin]*
1, 7, 7-Trimethylbicyclol[2.2.1]heptan-2-ol (*Isocamphol, Isobornyl alcohol*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/124-76-5 Skin/eye irritant http://www.thegoodscentscompany.com/data/rw1002092.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *R 42/43 - May cause sensitization by inhalation and skin contact.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
1-Acetonaphthone	Y		https://pubchem.ncbi.nlm.nih.gov/compound/1 -Acetonaphthone#section=Safety-and-Hazards GHS Hazard Statements *H315 (11.59%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (80.69%): May cause an allergic skin reaction [Warning Sensitization, Skin]*
1-Benzazole (*Indole*)	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/798#section=Safety-and-Hazards GHS Hazard Statements *H311 (98.88%): Toxic in contact with skin [Danger Acute toxicity, dermal]* https://chem.nlm.nih.gov/chemidplus/rn/120-72-9 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1006511.html#tosafty European information : Most important hazard(s):

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			R 21/22 - Harmful in contact with skin and if swallowed. *R 37/38 - Irritating to respiratory system and skin.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
1-Cedr-8-en-9-yl ethenone (*Methyl cedryl ketone, vertofix*)	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/107065#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (94.26%): May cause an allergic skin reaction [Warning Sensitization, Skin]* http://www.thegoodscentscompany.com/data/rw1026472.html#tosafty European information : Most important hazard(s): Xi - Irritant *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.*
1-Methoxy-4-methylbenzene (*p-methylanisole*)		Y	https://pubchem.ncbi.nlm.nih.gov/compound/7731#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (99.65%): Causes skin irritation [Warning Skin corrosion/irritation]* https://chem.nlm.nih.gov/chemidplus/rn/104-93-8 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1003932.html#tosafty European information : Most important hazard(s): *R 38 - Irritating to skin.* S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
1-Methyl-1-(4-methylcyclohex-3-en-1-yl)ethyl acetate (*alpha-Terpinyl acetate*)	Y		http://www.thegoodscentscompany.com/data/rw1011272.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* GHS Label elements, including precautionary statements Signal word Warning Hazard statement(s)

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			H315 - Causes skin irritation
2,6-Dimethylheptan-2-ol (*2,6-Dimethyl-2-heptano Freesia heptanol Dimetol (Givaudan)l*)		Y	https://pubchem.ncbi.nlm.nih.gov/compound/83268#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* https://chem.nlm.nih.gov/chemidplus/rn/13254-34-7 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1024471.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
2-Isopropenyl-5-methylcyclohexanol (*Isopulegol*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/24585#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (82.31%): Causes skin irritation [Warning Skin corrosion/irritation]* http://www.thegoodscentscompany.com/data/rw1449811.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
2-Isopropyl-5-methylcyclohexanol (*Menthol, Menthol, (1 alpha, 2 beta, 5 alpha)-Isomer*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/1254#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (97.9%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard SYMPTOMS: Symptoms of exposure to this compound may include irritation of the skin, eyes, mucous membranes and upper respiratory tract. from CAMEO Chemicals https://chem.nlm.nih.gov/chemidplus/rn/89-78-1 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1029672.html#tosafty European information : Most important hazard(s): Xi - Irritant *R 37/38 - Irritating to respiratory system and skin.* R 41 - Risk of serious damage to eyes. S 24/25 - Avoid contact with skin and eyes.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
2-Nonanone,3-(hydroxymethyl) (*2-Acetyl-1-octanol* *Herbal ketone* *Methyl lavender ketone -* (IFF))		Y	https://pubchem.ncbi.nlm.nih.gov/compound/106823#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]*
2-Octanol,2,6-dimethyl (*2,6-Dimethyloctan-2-ol*)		Y	https://pubchem.ncbi.nlm.nih.gov/compound/86751#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* http://www.thegoodscentscompany.com/data/rw1030292.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
2-Phenylethyl 3-methylbutanoate (*Phenethyl Isovalerate*)	Y		 http://www.thegoodscentscompany.com/data/rw1010091.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
2-Phenylethyl formate (*Phenethyl formate* *formic acid, 2-phenylethyl ester*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7711#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin] http://www.thegoodscentscompany.com/data/rw1026431.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes.
2-Phenylethyl phenylacetate (*Phenethyl phenylacetate*)	Y		http://www.thegoodscentscompany.com/data/rw1010111.html#tosafty European information : Most important hazard(s): *Xi N - Irritant, Dangerous for the environment.* *R 36/38 - Irritating to skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td>2-Propanol, 1,1 '-oxybis-</td><td>Y</td><td>Y</td><td>https://chem.nlm.nih.gov/chemidplus/rn/110-98-5
Skin/eye irritant

https://pubchem.ncbi.nlm.nih.gov/compound/8087#section=Safety-and-Hazards
Signal: Warning
GHS Hazard Statements

H315 (97.83%): Causes skin irritation [Warning Skin corrosion/irritation]

Skin, Eye, and Respiratory Irritations
A skin and eye irritant.
Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2805
from HSDB

Skin Symptoms
Redness.
from ILO-ICSC

NIOSH Toxicity Data
<table>
<tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr>
<tr><td>Skin and Eye Irritation</td><td></td><td>eye /rabbit</td><td>500 mg</td><td>mild</td><td>October 2010</td></tr>
<tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>500 µL/24H</td><td>moderate</td><td>October 2010</td></tr>
</table></td></tr>
<tr><td>2-t-Butylcyclohexyl Acetate (2-Tert-Butylcyclohexyl acetate

Green acetate

Verdox (IFF))</td><td></td><td>Y</td><td>http://www.thegoodscentscompany.com/data/rw1002462.html#tosafty
Most important hazard(s):

S 24/25 - Avoid contact with skin and eyes.

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>3-(5,5,6-Trimethylbicyclol[2,2.1]hept-2-yl)cyclohexanol

(3-(5,5,6-Trimethyl-2-norbornyl)cyclohexanol

Sandal hexanol

Sandiff (IFF))</td><td>Y</td><td></td><td>https://pubchem.ncbi.nlm.nih.gov/compound/103005#section=Safety-and-Hazards
Signal: Warning
GHS Hazard Statements

H315 (95.2%): Causes skin irritation [Warning Skin corrosion/irritation]

http://www.thegoodscentscompany.com/data/rw1006491.html#tosafty
European information :
Most important hazard(s):
S 24/25 - Avoid contact with skin and eyes.</td></tr>
<tr><td>3, 7-Dimethyloct-6-en-l-ol

(Citronellol)</td><td>Y</td><td>Y</td><td>https://pubchem.ncbi.nlm.nih.gov/compound/8842#section=Safety-and-Hazards
Signal: Warning
GHS Hazard Statements</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			H315 (95.35%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (99.55%): May cause an allergic skin reaction [Warning Sensitization, Skin] Skin, Eye, and Respiratory Irritations */Skin/ moderately irritating.* Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 235 from HSDB Toxicity Summary HUMAN EXPOSURE AND TOXICITY: Adult male volunteers with no known allergic reactions were patch-tested on their back for 48 hr with 32% citronellol. After 48 hr, patches were removed and the skin was cleaned of any residual test material. Moderate irritation was observed. A patch test using a 1% concentration of citronellol in acetone gave a positive reaction in subjects allergic to citronella oil. ANIMAL STUDIES: Citronellol applied full strength to intact or abraded rabbit skin for 24 hr under occlusion was moderately irritating. Severe irritation was observed in rabbits and guinea pigs exposed to 100% compound (unoccluded) for 24, 48 or 72 hr. from HSDB https://chem.nlm.nih.gov/chemidplus/rn/106-22-9 *Skin/eye irritant* https://www.ewg.org/guides/substances/1285-CITRONELLOL#.W38ssuhKiUk Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance shows some evidence of causing contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/citronellol-0 The safety of Citronellol has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Citronellol in fragrances because of potential sensitization. http://www.thegoodscentscompany.com/data/rw1007032.html#tosafty European information : Most important hazard(s): *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
3, 7-Dimethylocta-2,6-dien-1-yl acetate	Y		Neryl Acetate

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
(*Neryl Acetate* *Nerol Acetate*)			https://pubchem.ncbi.nlm.nih.gov/compound/1549025#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (15.29%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (15.29%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Skin, Eye, and Respiratory Irritations In human patch test, geraniol @ 32% concn was severely irritating & geranyl acetate mildly irritating. Motoyoski et al; Cosmet Toiletries 94(8): 41 (1979) from HSDB http://www.thegoodscentscompany.com/data/rw1033552.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.*
3,7-Dimethylocta-2,6-dien-1-yl benzoate (*Trans-3,7-Dimethylocta-2,6-dien-1-yl benzoate,* *Geranyl Benzoate*)	Y		Trans-3,7-Dimethylocta-2,6-dien-1-yl benzoate or Geranyl Benzoate ???? https://pubchem.ncbi.nlm.nih.gov/compound/5353011#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* http://www.thegoodscentscompany.com/data/rw1024871.html#tosafty European information : Most important hazard(s): S 24/25 - Avoid contact with skin and eyes.
3-Methyl-1H-indole (*Skatole*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/6736#section=GHS-Classification Signal: Warning GHS Hazard Statements with hazard statement code(s): *H315 (96.3%): Causes skin irritation [Warning Skin corrosion/irritation]* http://www.thegoodscentscompany.com/data/rw1006331.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* S 20/21 - When using do not eat, drink or smoke. S 24/25 - Avoid contact with skin and eyes.
3-Methyl-5-(2,2,3-trimethylcyclopent-3-en-1-yl)pentan-2-ol (*Sandal pentanol, Sandalore*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/103212#section=Safety-and-Hazards Signal: Warning http://www.thegoodscentscompany.com/data/rw1026291.html#tosafty European information : Most important hazard(s):

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Xi - Irritant *R 36/37/38 - Irritating to eyes, respiratory system, and skin.*
3-Methylbutyl salicylate (*Isoamyl Salicylate*)		Y	http://www.thegoodscentscompany.com/data/rw1006772.html#tosafty
3-Phenylpropan-1-ol	Y		https://pubchem.ncbi.nlm.nih.gov/compound/31234#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (98.51%): Causes skin irritation [Warning Skin corrosion/irritation]* Toxicity Summary HUMAN EXPOSURE AND TOXICITY: In a multicenter study, 218 fragrance sensitive patients with proven contact dermatitis were patch tested. Reactions (0.9%) in fragrance sensitive patients were observed with 3-phenylpropanol at 5% in petrolatum. ANIMAL STUDIES: In an irritation study in rabbits 3-phenylpropanol was applied for 24 hr under occlusion at dose levels of 2.5 and 5 g/kg. At 2.5 g/kg, moderate erythema and slight to moderate edema were observed. At 5 g/kg, moderate to severe erythema and moderate edema were observed. In another study in rabbits, 3-phenyl-1-propanol was applied for 24 hr under occlusion at 5 g/kg. Moderate to severe erythema, severe edema, scaling and necrosis were observed. A 0.5 mL aliquot of 3-phenylpropanol was applied to intact and abraded skin for 24 hr under occlusion. Moderate irritation was observed. Necrosis was also observed. from HSDB https://chem.nlm.nih.gov/chemidplus/rn/122-97-4 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1010172.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
4-(2,6,6-Trimethylcyclohex-2-en-1-yl)but-3-en-2-one (*alpha-ionone*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/5282108#section=Safety-and-Hazards Signal: Danger GHS Hazard Statements Skin, Eye, and Respiratory Irritations *alpha-Ionone was found to be a moderate /skin/ irritant.* Lalko J et al; Food Chem Toxicol 45 Suppl 1: S235-40 (2007) from HSDB Toxicity Summary *HUMAN EXPOSURE AND TOXICITY: AI (32 % in acetone) was found to be a moderate irritant*. No reactions were observed with 1% AI; 5% AI produced one irritant/questionable reaction. ANIMAL STUDIES: No skin irritation was observed in miniature swine using neat AI. In guinea pigs AI was reported to be *moderately irritating in skin test*. AI produced *severe skin irritation reaction in rabbits*. AI was tested in a 90-days oral toxicity study using male and female rats.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			from HSDB http://www.thegoodscentscompany.com/data/rw1011952.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *R 42/43 - May cause sensitization by inhalation and skin contact.* S 24/25 - Avoid contact with skin and eyes.
4,7-Methano-IH-indenol, 3a,4,5,6, 7, 7a-hexahydro-, propanoate (*Tricyclodecenyl Propionate*)		Y	https://pubchem.ncbi.nlm.nih.gov/compound/86579#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements https://chem.nlm.nih.gov/chemidplus/rn/17511-60-3 *Skin/eye irritant* https://www.ewg.org/guides/substances/6105-TRICYCLODECENYLPROPIONATE#.W4QRzuhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance lacks data on contact allergy in humans. lOpinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1011151.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
4-Methyl phenyl 2-methylpropanoate (*p-Tolyl isobutyrate* *P-Cresyl isobutyrate*)	Y		http://www.thegoodscentscompany.com/data/rw1035021.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin.
5-Isopropenyl-2-methylcyclohex-2-en-1-one (*Carvone*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7439#section=Hazards-Identification Signal: Danger GHS Hazard Statements *H315 (99.37%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (92.11%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Toxicity Summary HUMAN EXPOSURE AND TOXICITY: The sensitizing potential of l-carvone has been considered low, but it has occasionally caused contact allergy in users of spearmint toothpaste and chewing gum. ANIMAL STUDIES: Clinical signs after acute exposure in mice and rats were different depending on the route of exposure.. After acute dermal exposure no systemic or skin effects were observed from HSDB
8-Cyclohexadecen-1-one	Y		https://pubchem.ncbi.nlm.nih.gov/compound/534634#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (68.75%): Causes skin irritation [Warning Skin corrosion/irritation]*

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td>Acetic acid, p-tert-butylcyclohexyl

(4-Tert-butylcyclohexyl acetate)</td><td></td><td>Y</td><td>https://chem.nlm.nih.gov/chemidplus/rn/32210-23-4
Skin/eye irritant

http://www.thegoodscentscompany.com/data/rw1001372.html#tosafty

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>Acetic acid, phenylmethyl ester

(Benzyl acetate)</td><td>Y</td><td></td><td>https://pubchem.ncbi.nlm.nih.gov/compound/8785#section=Hazards-Identification
Signal: Danger
GHS Hazard Statements

H315: Causes skin irritation [Warning Skin corrosion/irritation]

Health Hazard
Harmful if inhaled. May be harmful if swallowed or absorbed through the skin. Vapor or mist is irritating to the eyes, mucous membrane and upper respiratory tract. (USCG, 1999)
from CAMEO Chemicals

Skin, Eye, and Respiratory Irritations
... Irritating to skin, eyes, respiratory tract.
Budavari, S. (ed.). The Merck Index - Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc., 1989., p. 176
from HSDB

NIOSH Toxicity Data
<table><tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>100 mg/24H</td><td>moderate</td><td>October 2017</td></tr></table>
Skin Symptoms
Dry skin.
from ILO-ICSC

https://chem.nlm.nih.gov/chemidplus/rn/140-11-4
Skin/eye irritant

https://www.ewg.org/guides/substances/640-BENZYLACETATE#.W4QdrehKiUk
The European Commission's Scientific Committee on Consumer Safety reports this substance shows negative results for causing contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive

http://www.thegoodscentscompany.com/data/rw1001612.html#tosafty
European information :
Most important hazard(s):
Xi - Irritant
R 36/37/38 - Irritating to eyes, respiratory system, and skin.</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Aldehyde C-7 (*Heptanal*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8130#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (99.71%): Causes skin irritation [Warning Skin corrosion/irritation]* https://chem.nlm.nih.gov/chemidplus/rn/111-71-7 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1014291.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 50/53 - Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.
Alpha-Isomethyl Ionone	Y		https://pubchem.ncbi.nlm.nih.gov/compound/5372174#section=Hazards-Identification Signal: Warning GHS Hazard Statements H315 (80.27%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (90.98%): May cause an allergic skin reaction [Warning Sensitization, Skin] http://www.thegoodscentscompany.com/data/rw1594731.html#tosafty (50% minimum alpha-isomethyl ionone) European information : Most important hazard(s): *Xi N - Irritant, Dangerous for the environment.* *R 38 - Irritating to skin.* *R 43 - May cause sensitisation by skin contact.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin sensitisation (Category 1), H317* (70% minimum alpha-isomethyl ionone) European information : Most important hazard(s): *Xi - Irritant* *R 38 - Irritating to skin.* 02 - Keep out of the reach of children. S 24/25 - Avoid contact with skin and eyes. (80% minimum alpha-isomethyl ionone) European information : Most important hazard(s): *Xi - Irritant* *R 38 - Irritating to skin.* S 24/25 - Avoid contact with skin and eyes.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			(90% minimum alpha-isomethyl ionone) European information : Most important hazard(s): *Xi - Irritant* *R 38 - Irritating to skin.* S 24/25 - Avoid contact with skin and eyes. https://cosmeticsinfo.org/ingredient/alpha-isomethyl-ionone-0 The safety of Alpha-Isomethyl Ionone has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of mixed isomers of methyl ionone (including Alpha-Isomethyl Ionone) in fragrances because of potential sensitization. The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Alpha-Isomethyl Ionone and determined that it was Generally Recognized as Safe (GRAS) for use as a flavoring substance. In Europe, Alpha-Isomethyl Ionone is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Alpha-Isomethyl Ionone must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 https://www.ewg.org/skindeep/ingredient/700295/ALPHA-ISOMETHYL_IONONE/#.W4QmbOhKiUl Allergies/immunotoxicity Possible human immune system toxicant or allergen SCCPNFP (Scientific Committee On Cosmetic Products And Non-Food Products). 1999. Opinion Concerning Fragrance Allergy In Consumers. . SCCNFP/0017/98 Final, December 1999; and SCCPNFP (Scientific Committee On Cosmetic Products And Non-Food Products). 2000. An Initial List Of Perfumery Materials Which Must Not Form Part Of Fragrances Compounds Used In Cosmetic Products. SCCNFP/0320/00, final May 2000.
Amyl Cinnamal (*alpha-Amyl cinnamaldehyde* *alpha-pentylcinnamaldehyde*)	Y	Y	https://chem.nlm.nih.gov/chemidplus/rn/122-40-7 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/1623625#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements H317 (98.8%): May cause an allergic skin reaction [Warning Sensitization, Skin] Skin, Eye, and Respiratory Irritations *A severe skin irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 251 from HSDB

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			https://www.ewg.org/guides/substances/368-AMYLCINNAMALDEHYDE#.W4QozuhKiUk Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive EPA's review of industry submitted toxicity data and the potential for human exposure concludes that this substance poses a moderate risk for human health. EPA Hazard-Based Prioritizations - Risks - Environmental Protection Agency (EPA) https://cosmeticsinfo.org/ingredient/amyl-cinnamal-0 The safety of Amyl Cinnamal has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Amyl Cinnamal in fragrances because of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for alpha-amyl cinnamic aldehyde (Amyl Cinnamal): https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=cinnamaldehyde The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Amyl Cinnamal does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Amyl Cinnamal: http://www.inchem.org/documents/jecfa/jeceval/jec_123.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Amyl Cinnamal and determined that it was Generally Recognized as Safe for use as a flavoring substance. In Europe, Amyl Cinnamal is included on the list of "allergenic" substances. The European Cosmetics Directive requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Amyl Cinnamal must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1001011.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* R 43 - May cause sensitisation by skin contact. Hazards identification GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) Skin sensitisation (Category 1), H317
Anisaldehyde	Y		https://chem.nlm.nih.gov/chemidplus/rn/123-11-5

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
(*P-Anisaldehyde*)			*Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1001272.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/38 - Irritating to skin and eyes. Hazards identification GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Acute toxicity, dermal (Category 5), H313* *Skin corrosion/irritation (Category 3), H316*
Benzaldehyde	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr348.pdf https://chem.nlm.nih.gov/chemidplus/rn/100-52-7 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/240#section=GHS-Classification Signal: Warning GHS Hazard Statements *H312 (52%): Harmful in contact with skin [Warning Acute toxicity, dermal]* *H315 (48%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard Inhalation of concentrated vapor may irritate eyes, nose and throat. Liquid is irritating to the eyes. *Prolonged contact with the skin may cause irritation. (USCG, 1999)* from CAMEO Chemicals Skin, Eye, and Respiratory Irritations *A skin irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 353 from HSDB NIOSH Toxicity Data Measurement / System / Route/Organism / Dose / Effect / Date Skin and Eye Irritation / / skin /rabbit / 500 mg/24H / moderate / April 2017 Health Effects *Irritation-Eyes, Nose, Throat, Skin---Moderate (HE15)* from OSHA Chemical Sampling Information Symptoms Irritation of eyes, skin, nose, throat; contact dermatitis; INGES. ACUTE: sore throat

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			from OSHA Chemical Sampling Information Skin Symptoms Redness. from ILO-ICSC Toxicity Summary HUMAN EXPOSURE AND TOXICITY: It may cause contact dermatitis.. ANIMAL STUDIES: from HSDB https://www.ewg.org/guides/substances/7337-BENZALDEHYDE#.W4QxU-hKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/benzaldehyde-0 FDA: Link to the Code of Federal Regulations for Benzaldehyde https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.60&SearchTerm=benzaldehyde Benzaldehyde may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 The Joint FAO/WHO Expert Committee on Food Additives has established an Acceptable Daily Intake of 0-5 mg Benzaldehyde/kg body weight. No safety concern was indicated at current levels of intake when used as a flavoring agent. http://www.inchem.org/documents/jecfa/jeceval/jec_176.htm http://www.thegoodscentscompany.com/data/rw1001491.html#tosafty European information : Most important hazard(s): Xn - Harmful. S 24 - Avoid contact with skin. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Benzaldehyde, 2-hydroxy- (*Salicylaldehyde*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/6998#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H312 (49.04%): Harmful in contact with skin [Warning Acute toxicity, dermal]* *H315 (53.07%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard LIQUID: Irritating to skin and eyes. Harmful if swallowed. (USCG, 1999) from CAMEO Chemicals

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			https://chem.nlm.nih.gov/chemidplus/rn/90-02-8 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1028641.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 21/22 - Harmful in contact with skin and if swallowed.* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Benzene, 1,3-dimethoxy- (*meta-dimethyl hydroquinone* *m-dimethoxybenzene*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/9025#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H312 (50%): Harmful in contact with skin [Warning Acute toxicity, dermal]* *H315 (50%): Causes skin irritation [Warning Skin corrosion/irritation]* http://www.thegoodscentscompany.com/data/rw1027111.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Benzene, ethenyl- (*Styrene, vinylbenzene*)	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR673.pdf https://chem.nlm.nih.gov/chemidplus/rn/100-42-5 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/styrene#section=Safety-and-Hazards Signal: Danger GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard *Moderate irritation of eyes and skin*. High vapor concentrations cause dizziness, drunkeness, and anesthesia. (USCG, 1999) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations *Irritating to skin ...* Commission of the European Communities. Legislation on Dangerous Substances - Classification and Labelling in the European Communities. Vol. II. London and Trotman Ltd., 1989., p. 224 from HSDB NIOSH Toxicity Data

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Measurement</td><td>Date</td><td>System</td><td>Route/Organism</td><td>Dose</td><td>Effect</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>eye /human</td><td>50 ppm</td><td>mild</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>eye /rabbit</td><td>100 mg</td><td>severe</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>eye /rabbit</td><td>100 mg/24H</td><td>moderate</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /human</td><td>500 mg rinse</td><td></td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /rabbit</td><td>500 mg open irritation test</td><td>mild</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /rabbit</td><td>100%</td><td>moderate</td></tr>
</table>
Skin Symptoms
Redness. Pain.
from ILO-ICSC</td></tr>
<tr><td>Benzeneacetic acid

(Phenylacetic Acid)</td><td>Y</td><td></td><td>https://pubchem.ncbi.nlm.nih.gov/compound/999#section=Toxicity

NIOSH Toxicity Data
Skin and Eye Irritation November 2009 eye /rabbit 100 mg/24H moderate

Skin Symptoms
Redness.
from ILO-ICSC

Toxicity Summary
HUMAN STUDIES: Inhalation exposure leads to cough, sore throat.Skin exposure leads to redness.
from HSDB

http://www.thegoodscentscompany.com/data/rw1009911.html#tosafty
European information :
Most important hazard(s):
Xi - Irritant
R 36/37/38 - Irritating to eyes, respiratory system, and skin.
S 24/25 - Avoid contact with skin and eyes.

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>Benzeneacetic acid, methyl ester</td><td>Y</td><td></td><td>https://chem.nlm.nih.gov/chemidplus/rn/101-41-7
Skin/eye irritant</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
(*Methyl 2-Phenylacetate* *Methyl phenylacetate*)			https://pubchem.ncbi.nlm.nih.gov/compound/7559#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (66.67%): Causes skin irritation [Warning Skin corrosion/irritation]* Skin, Eye, and Respiratory Irritations *A skin irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2388 from HSDB http://www.thegoodscentscompany.com/data/rw1008431.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Acute toxicity, dermal (Category 5), H313* *Skin corrosion/irritation (Category 3), H316*
Benzoic acid, 2,4-dihydroxy-3,6-dimethyl-, methyl ester (*Methyl 3-methylorsellinate*)	Y		http://www.thegoodscentscompany.com/data/rw1023372.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* H335
Benzoic acid, 2-hydroxy-, 2-methylpropyl ester (*Isobutyl Salicylate*)	Y		http://www.thegoodscentscompany.com/data/rw1006892.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.*
Benzoic acid, 2-hydroxy-, ethyl ester (*Ethyl salicylate*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/118-61-6 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1001561.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* S 24/25 - Avoid contact with skin and eyes.
Benzophenone		Y	Benzophones-1, -3, -4, -5, -9, and -11

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PRN475.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr219.pdf https://cosmeticsinfo.org/ingredient/benzophenone-1 The Food and Drug Administration (FDA) has approved the use of Benzophenone-3 and Benzophenone-4 as safe and effective, over-the-counter (OTC) sunscreen ingredients. When used as a sunscreen ingredient in the United States, Benzophenone-3 is called Oxybenzone, and may be used at concentrations up to 6%, and Benzophenone-4 is called Sulisobenzone, and may be used at concentrations up to 10%. FDA: Link to Code of Federal Regulations for Benzophenone-3 (Oxybenzone) and Benzophenone-4 (Sulisobenzone) https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=352&showFR=1 Benzophenone-3, listed as Oxybenzone, and Benzophenone-4 and -5, listed as Sulisobenzone and Sulisobenzone Sodium, respectively, are included in Annex VII, Part 1 (UV filter which cosmetic products may contain) of the Cosmetics Directive of the European Union. Oxybenzone may be used at concentrations up to 10%, and products containing 0.5% Oxybenzone when used in sunscreen products must be labeled "contains Oxybenzone." Sulisobenzone and Sulisobenzone Sodium may be used at concentrations up to 5% as Sulisobenzone. There are studies that suggest that some sunscreen ingredients, including Oxybenzone may have activity like the hormone, estrogen. Therefore, the European Commission's Scientific Committee for Cosmetic Products and Non-Food Products Intended for Consumers (SCCNFP) was asked to consider if UV filters as used in sunscreen products have estrogenic effects which have the potential to affect human health. The SCCNFP concluded that UV filters used in sunscreen products allowed in the European market have no estrogenic effects that could potentially affect human health. https://pubchem.ncbi.nlm.nih.gov/compound/3102#section=Exposure-Routes Skin Symptoms Redness. from ILO-ICSC http://www.thegoodscentscompany.com/data/rw1016332.html#tosafty European information : Most important hazard(s): *Xi N - Irritant, Dangerous for the environment.* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.*
Benzyl Alcohol	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr323.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr323.pdf https://chem.nlm.nih.gov/chemidplus/rn/100-51-6 Skin/eye irritant https://pubchem.ncbi.nlm.nih.gov/compound/244#section=Hazards-Identification Signal: Warning GHS Hazard Statements H312 (17.85%): Harmful in contact with skin [Warning Acute toxicity, dermal] Skin, Eye, and Respiratory Irritations A moderate skin and severe eye irritant.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower

Chemical	Baby Powder	Shower-to-Shower	
			Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 399 from HSDB *It is slightly irritating to the skin* International Labour Office. Encyclopedia of Occupational Health and Safety. Vols. I&II. Geneva, Switzerland: International Labour Office, 1983., p. 111 from HSDB Vapor: Irritating to eyes, nose and throat. Liquid: Irritating to skin & eyes. U.S. Coast Guard, Department of Transportation. CHRIS - Hazardous Chemical Data. Volume II. Washington, D.C.: U.S. Government Printing Office, 1984-5. from HSDB NIOSH Toxicity Data

Measurement	System	Route/Organism	Dose	Effect	Date
Skin and Eye Irritation		skin /human	1%/2D		April 2017
Skin and Eye Irritation		skin /man	16 mg/48H	mild	April 2017
Skin and Eye Irritation		skin /pig	100%	moderate	April 2017
Skin and Eye Irritation		skin /rabbit	100 mg/24H	moderate	April 2017

Skin Symptoms
Redness.
from ILO-ICSC

Toxicity Summary
Toxicity
1250 mg/kg (rat, oral) LD50 400 mg/kg IPR-RAT LD50 2000 mg/kg SKN-RBT LD50 53 mg/kg IVN-RAT LD50 2500 mg/kg ORL-GPG LD50
from DrugBank

HUMAN EXPOSURE AND TOXICITY: Benzyl alcohol has been found to be irritating to the skin at levels 3% or greater. Patch test with 0.65% benzyl alcohol did not produce irritation of the skin. ANIMAL STUDIES: In a primary irritation study 10% benzyl alcohol applied in a 24-hour occlusive patch to the back of eight male albino rabbits did not cause irritation. Undiluted benzyl alcohol was moderately irritating when applied to the depilated skin of guinea pigs for 24 hr.
from HSDB

https://www.ewg.org/guides/substances/641-BENZYLALCOHOL#.W4RkHehKiUk
Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/benzyl-alcohol The Food and Drug Administration (FDA) includes Benzoic Acid and Sodium Benzoate on its list of direct food substances affirmed as Generally Recognized As Safe (GRAS). The safety of Benzyl Alcohol and Benzyl Benzoate has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on these evaluations, International Fragrance Association (IFRA) Standards have been established. The IFRA standards restrict the use of Benzyl Alcohol and Benzyl Benzoate in fragrances because of potential sensitization. More safety Information: Clinical data indicated that in a few individuals these ingredients produced non-immunologic contact urticaria and non-immunologic immediate contact reactions, characterized by the appearance of wheals, erythema, and pruritis. In one study, 5% Benzyl Alcohol elicited a reaction, and in another study, 2% Benzoic Acid did likewise. Benzyl Alcohol, however, was not a sensitizer at 10%, nor was Benzoic Acid a sensitizer at 2%. Recognizing that the non-immunologic reactions were strictly cutaneous, likely involve a cholinergic mechanism, it was concluded that these ingredients could be used safely at concentrations up to 5%. Additionally, Benzyl Alcohol was considered safe at up to 10% for use in hair dyes. The limited body exposure, the duration of use, and the frequency of use were considered in concluding that the non-immunologic reactions would not be a concern. Link to FDA Code of Federal Regulations and the Federal Register for Benzyl Alcohol https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=benzyl%20alcohol Benzyl Alcohol may be used as a preservative in cosmetics and personal care products marketed in the European Union at a maximum concentration of 1%. Benzoic Acid and its salts and esters are also permitted for use as preservatives in cosmetics and personal care products at a maximum concentration (expressed as the acid) of 2.5% in rinse-off products (except oral care products), 1.7% in oral care products and 0.5% in leave on products (see Annex VI). Benzyl Alcohol and Benzyl Benzoate are also listed in in Annex III of the European Union Cosmetics Directive.When Benzyl Alcohol or Benzyl Benzaote are used as fragrance ingredients, Annex III requires that the presence of these fragrance ingredients be indicated on the label of the product when used at greater than 0.001% in leave-on products, and greater than 0.01% in rinse-off products. The Joint FAO/WHO Expert Committee on Food Additives has established an Acceptable Daily Intake of 0-5 mg/kg for the sum of Benzoic Acid, Potassium and Sodium Benzoate: http://www.inchem.org/documents/jecfa/jecmono/40abcj02.htm
Benzyl Benzoate	Y	Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR574.pdf https://pubchem.ncbi.nlm.nih.gov/compound/2345#section=Fire-Hazard Skin, Eye, and Respiratory Irritations Benzyl benzoate is relatively nontoxic but may irritate the skin and eyes.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			American Medical Association, Council on Drugs. AMA Drug Evaluations Annual 1994. Chicago, IL: American Medical Association, 1994., p. 1615 from HSDB Skin Symptoms MAY BE ABSORBED! Dry skin. Redness. from ILO-ICSC https://www.ewg.org/guides/substances/642-BENZYLBENZOATE#.W4RnX-hKiUk Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/benzyl-benzoate SEE BENZYL ALCOHOL
Benzyl Salicylate	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/8363#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements H317 (95.53%): May cause an allergic skin reaction [Warning Sensitization, Skin] H319 (72.34%): Causes serious eye irritation [Warning Serious eye damage/eye irritation] NIOSH Toxicity Data Measurement | Date | System | Route/Organism | Dose | Effect Skin and Eye Irritation | April 2015 | | skin /human | 2%/2D | https://www.ewg.org/guides/substances/645-BENZYLSALICYLATE#.W4RwP-hKiUk Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/benzyl-salicylate-0 The Food and Drug Administration (FDA) has approved the use of Benzyl Salicylate as a flavoring agent for direct addition to food. The safety of Benzyl Salicylate has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Benzyl Salicylate in fragrances because of potential sensitization. More safety Information: See the FDA Code of Federal Regulations for Benzyl Salicylate: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=172.515

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Benzyl Salicylate does not present a safety concern at current levels of intake when used as a flavoring agent. http://www.inchem.org/documents/jecfa/jeceval/jec_215.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Benzyl Salicylate and determined that it is Generally Recognized as Safe (GRAS) for use as a flavoring substance. In Europe, Benzyl Salicylate is included on the list of "allergenic" substances. The European Cosmetics Directive requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Benzyl Salicylate must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0012 http://www.thegoodscentscompany.com/data/rw1001792.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *R 43 - May cause sensitisation by skin contact.* S 24 - Avoid contact with skin. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) Skin sensitisation (Category 1), H317
Boswellia Carterii Oil (*Oils, olibanum Frankincense oil*)	Y		No Data http://www.thegoodscentscompany.com/data/es1004051.html#tosafty European information : Most important hazard(s): Xn - Harmful. R 10 - Flammable. *R 20/21/22 - Harmful by inhalation, in contact with skin and if swallowed.* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* R 42/43 - May cause sensitization by inhalation and skin contact. S 24/25 - Avoid contact with skin and eyes.
Butanoic acid, ethyl ester (*Ethyl n-butyrate* *Ethyl butanoate*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/105-54-4 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1004792.html#tosafty European information : Most important hazard(s): Xi - Irritant R 10 - Flammable. R 36/37/38 - Irritating to eyes, respiratory system, and skin. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Butanoic acid, pentyl ester (*Amyl Butyrate*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/10890#section=Health-Hazard

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Excerpt from ERG Guide 130 [Flammable Liquids (Water-Immiscible / Noxious)]: May cause toxic effects if inhaled or absorbed through skin. Inhalation or contact with material may irritate or burn skin and eyes. Fire will produce irritating, corrosive and/or toxic gases. Vapors may cause dizziness or suffocation. Runoff from fire control or dilution water may cause pollution. (ERG, 2016) from CAMEO Chemicals http://www.thegoodscentscompany.com/data/rw1004151.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin.
Camphor	Y		https://pubchem.ncbi.nlm.nih.gov/compound/2537#section=Hazards-Identification Signal: Danger GHS Hazard Statements H312 (10.82%): Harmful in contact with skin [Warning Acute toxicity, dermal] H315 (16.04%): Causes skin irritation [Warning Skin corrosion/irritation] Health Hazard Excerpt from ERG Guide 133 [Flammable Solids]: Fire may produce irritating and/or toxic gases. Contact may cause burns to skin and eyes. Contact with molten substance may cause severe burns to skin and eyes. Runoff from fire control may cause pollution. (ERG, 2016) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations The substance is irritating to the eyes, the skin, and the respiratory tract. International Program on Chemical Safety/ Commission of the European Union; International Chemical Safety Card on Camphor. (May 2003). Available from, as of June 30, 2014: http://www.inchem.org/documents/icsc/icsc/eics1021.htm from HSDB Health Effects Irritation-Eye, Nose, Throat, Skin---Moderate (HE15) Acute Toxicity---short-term high hazard effects (HE4) CNS Effects (HE7) from OSHA Chemical Sampling Information Symptoms Irritation of eyes, skin, mucous membrane; nausea, vomiting, diarrhea; headache, dizziness, excitement, epileptiform convulsions; cough, sore throat; Ingestion Acute: Burning sensation in throat and chest; GI symptoms; confusion, seizures, unconsciousness; Skin Absorption; Hepatotoxicity without GI symptoms. from OSHA Chemical Sampling Information irritation eyes, skin, mucous membrane; nausea, vomiting, diarrhea; headache, dizziness, excitement, epileptiform convulsions from The National Institute for Occupational Safety and Health (NIOSH) Skin Symptoms Redness. from ILO-ICSC https://cosmeticsinfo.org/ingredient/camphor-0

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The Food and Drug Administration (FDA) includes Camphor in its list of flavoring agents and related substances that are permitted for direct addition to food. Camphor is also approved for use as an active ingredient in Over-The-Counter (OTC) external analgesics, topical antitussive drug products and in anorectal products at concentrations of 0.1 to 3%. More safety Information: The International Programme on Chemical Safety has developed a monograph on the uses and potential effects of Camphor. Fairly large oral doses of Camphor are needed before adverse effects are observed. Carcinogenicity tests have been negative and Camphor is not mutagenic in bacteria. http://www.inchem.org/documents/pims/pharm/camphor.htm Natural Flavoring Substances: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.510&SearchTerm=camphor Antitussive Active Ingredients https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=341.14&SearchTerm=camphor Analgesic, Anesthetic, and Antipruritic Active Ingredients https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=346.16&SearchTerm=camphor Camphor may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 Health Canada permits the use of Camphor in cosmetics and personal care products at concentrations less than or equal to 3%. https://www.canada.ca/en/health-canada/services/cosmetics.html http://www.thegoodscentscompany.com/data/rw1056901.html#tosafty European information : Most important hazard(s): Xn - Harmful. R 20/21/22 - Harmful by inhalation, in contact with skin and if swallowed. R 36/37/38 - Irritating to eyes, respiratory system, and skin. R 40 - Limited evidence of a carcinogenic effect.
Caproic Acid	Y		https://chem.nlm.nih.gov/chemidplus/rn/142-62-1 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/8892#section=Hazards-Identification Signal: Danger GHS Hazard Statements *H311 (23.6%): Toxic in contact with skin [Danger Acute toxicity, dermal]* *H314 (100%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation]* Health Hazard Harmful if swallowed, inhaled, or absorbed through skin. Material is extremely destructive to tissue of mucous membranes and upper respiratory tract, eyes and skin. Inhalation may be fatal as a result of spasm, inflammation and edema of the larynx and bronchia, chemical pneumonitis and pulmonary edema. Symptoms of exposure may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea and vomiting. (USCG, 1999)

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			from CAMEO Chemicals NIOSH Toxicity Data Measurement | System | Route/Organism | Dose | Effect | Date Skin and Eye Irritation | | eye /rabbit | 750 µg | severe | October 2015 Skin and Eye Irritation | | skin /rabbit | 10 mg/24H open irritation test | mild | October 2015 Skin and Eye Irritation | | skin /rabbit | 465 mg open irritation test | mild | October 2015 Skin Symptoms Redness. Pain. from ILO-ICSC http://www.thegoodscentscompany.com/data/rw1008541.html#tosafty European information : Most important hazard(s): C - Corrosive. R 20/21/22 - Harmful by inhalation, in contact with skin and if swallowed. R 34 - Causes burns. S 24/25 - Avoid contact with skin and eyes. S 28 - After contact with skin, wash immediately with plenty of water.
Carum Carvi (Caraway) Fruit Oil	Y		https://chem.nlm.nih.gov/chemidplus/rn/8000-42-8 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/es1028851.html#tosafty European information : Most important hazard(s): Xi N - Irritant, Dangerous for the environment. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *R 43 - May cause sensitisation by skin contact.*
Cedrol	Y		https://pubchem.ncbi.nlm.nih.gov/compound/65575#section=GHS-Classification Skin, Eye, and Respiratory Irritations ...produced slight /skin/ irritation. Opdyke, D.L.J. (ed.). Monographs on Fragrance Raw Materials. New York: Pergamon Press, 1979., p. 205 from HSDB http://www.thegoodscentscompany.com/data/rw1003031.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* S 24/25 - Avoid contact with skin and eyes.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
Cedrus Atlantica (Cedarwood) Bark Oil	Y		https://chem.nlm.nih.gov/chemidplus/rn/8023-85-6 *Skin/eye irritant* https://www.ewg.org/guides/substances/1083-CEDRUSATLANTICAATLASCEDARBARKOIL#.W4SHeOhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Frangrance allergens in cosmetics (2011) - EU Cosmetics Directive
Cinnamal (*Cinnamaldehyde*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/104-55-2 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/637511#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard ACUTE/CHRONIC HAZARDS: Exposure to this chemical may cause irritation of the skin, eyes, upper respiratory tract and mucous membranes. (NTP, 1992) from CAMEO Chemicals SYMPTOMS: ACUTE/CHRONIC HAZARDS: This chemical may be harmful by inhalation, ingestion or skin absorption. It may cause irritation of the skin, eyes, upper respiratory tract, and mucous membranes. When heated to decomposition it may emit toxic fumes of carbon monoxide and carbon dioxide. (NTP, 1992) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations No primary dermal irritation was observed in human subjects exposed for 48 hours to a solution of a 3% active ingredient, while severe primary dermal irritation was observed in human subjects after exposure to 8% active ingredient. USEPA, Office of Pesticide Programs/ Ombudsman, Biopesticides and Pollution Prevention Division: Active Ingredient Fact Sheet for Cinnamaldehyde (040506) (December 2000). Available from, as of July 13, 2009: http://www.epa.gov/pesticides/biopesticides/ingredients/index_p-s.htm from HSDB Toxicological Information Health Effects Irritation-Eyes, Nose, Throat, Skin---Moderate (HE15); Allergic Contact Dermatitis (HE3) from OSHA Chemical Sampling Information Symptoms Irritation of eyes, skin, nose, throat; skin rash, itching; anaphylaxis (one case); INGES. ACUTE: Sore throat from OSHA Chemical Sampling Information Target Organs Eyes, skin, respiratory system from OSHA Chemical Sampling Information https://www.ewg.org/guides/substances/1258-CINNAMAL#.W4SOauhKiUk

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/cinnamal-0 The Food and Drug Administration (FDA) includes Cinnamal on its list of substances considered Generally Recognized As Safe (GRAS) for use as a synthetic flavoring substance. The safety of Cinnamal has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Cinnamal in fragrances because it of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for Cinnamal: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.60&SearchTerm=cinnamaldehyde The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Cinnamal does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Cinnamal: http://www.inchem.org/documents/jecfa/jeceval/jec_418.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Cinnamal and determined that it was Generally Recognized as Safe (GRAS) for use a flavoring substance. In Europe, Cinnamal is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Cinnamal must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1002632.html#tosafty European information : Most important hazard(s): Xn - Harmful. R 21/41 - Harmful in contact with skin, risk of serious damage to eyes. *R 38 - Irritating to skin.* *R 43 - May cause sensitisation by skin contact.* S 02 - Keep out of the reach of children. S 24 - Avoid contact with skin. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) Skin irritation (Category 2), H315 Skin sensitisation (Category 1), H317
Cinnamyl Alcohol (*3-Phenyl-2-propen-1-ol*)	Y	Y	https://chem.nlm.nih.gov/chemidplus/rn/104-54-1 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/5315892#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			H317 (96.97%): May cause an allergic skin reaction [Warning Sensitization, Skin] https://cosmeticsinfo.org/ingredient/cinnamyl-alcohol-0 The Food and Drug Administration (FDA) includes Cinnamyl Alcohol on its list of flavoring agents permitted for direct addition to food. The safety of Cinnamyl Alcohol has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Cinnamyl in fragrances because of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for Cinnamyl Alcohol: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=cinnamyl%20alcohol The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Cinnamyl Alcohol does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Cinnamyl Alcohol: http://www.inchem.org/documents/jecfa/jeceval/jec_422.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Cinnamyl Alcohol and determined that it was Generally Recognized as Safe (GRAS) for use as a flavoring substance. In Europe, Cinnamyl Alcohol is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Cinnamyl Alcohol must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1003292.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* S 24 - Avoid contact with skin. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Citral *(Geranial)*	Y		https://chem.nlm.nih.gov/chemidplus/rn/5392-40-5 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/638011#section=Hazards-Identification Signal: Danger GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (23.56%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			SYMPTOMS: Symptoms of exposure to this compound may include contact dermatitis. ACUTE/CHRONIC HAZARDS: This compound is a local irritant. When heated to decomposition it emits acrid smoke and fumes. (NTP, 1992) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations Irritant effect of 19 oils & 20 synthetic perfumes used in cosmetics were tested on skin of 50 male volunteers. Citral @ 32% concn was the most irritating of perfumes in human patch test. Motoyoshi k et al; Cosmet Toilet 94: 41 (197 from HSDB Irritating to skin. European Chemicals Bureau; IUCLID Dataset, Citral (CAS No. 5392-40-5). Available from, as of January 22, 2007: http://esis.jrc.ec.europa.eu/ from HSDB A cumulative irritation study was carried out on 8 volunteers. Patches were placed on the back daily, removed at 24 hr and read and them replaced with a fresh patch, over a period of 21 days. /Citral concentrations tested included 1, 4 and 8% in petrolatum./ The 8 % concentration was found to be a marginal irritant. European Chemicals Bureau; IUCLID Dataset, Citral (CAS No. 5392-40-5). Available from, as of January 22, 2007: http://esis.jrc.ec.europa.eu/ from HSDB During an investigation of an outbreak of dermatitis following the introduction of a lemon-scented detergent, citral was shown by patch tests to be a strong primary irritant if applied in association with heat; 10% citral induced slight responses at 23 deg C and pronounced responses at 43 deg C. Abstract: PubMed Rothenborg HW et al; Contact Dermatitis 3 (1): 37 (1977) from HSDB NIOSH Toxicity Data

Measurement	Date	System	Route/Organism	Dose	Effect
Skin and Eye Irritation	October 2017		skin /guinea pig	1%/48H	moderate
Skin and Eye Irritation	October 2017		skin /guinea pig	100 mg/24H	severe
Skin and Eye Irritation	October 2017		skin /human	2%/2D	
Skin and Eye Irritation	October 2017		skin /human	40 mg/24H	mild
Skin and Eye Irritation	October 2017		skin /man	16 mg/48H	severe
Skin and Eye Irritation	October 2017		skin /pig	50 mg/48H	severe

Ingredient List – Johnson's Baby Powder & Shower-to-Shower

Chemical	Baby Powder	Shower-to-Shower	

Skin and Eye Irritation	October 2017		skin /rabbit	500 mg/24H	moderate
Skin and Eye Irritation	October 2017		skin /rabbit	100 mg/24H	severe
Skin and Eye Irritation	October 2017		skin /woman	2%	

Skin Symptoms

Redness.
from ILO-ICSC

Toxicity Summary

Citral was rapidly absorbed from the gastro -intestinal tract. Much of an applied dermal dose was lost due to its extreme volatility, but the citral remaining on the skin was fairly well absorbed. Citral was rapidly metabolized and excreted as metabolites. Urine was the major route of elimination. Acute toxicity of this chemical is low in rodents because the oral or dermal LD50 values were more than 1000 mg/kg. This chemical is irritating to skin and not irritating to eyes in rabbits. There is some evidence that this chemical is a human skin sensitizer.
OECD; Screening Information Data Set for Citral, CAS # 5392-40-5 (2004). Available from, as of January 22, 2007: http://www.inchem.org/pages/sids.html

https://www.ewg.org/guides/substances/1279-CITRAL#.W4SeRehKiUk

Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive

The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive

https://cosmeticsinfo.org/ingredient/citral-0

The Food and Drug Administration (FDA) includes Citral in its list of substances considered Generally Recognized As Safe (GRAS) as a synthetic flavoring substance. The safety of Citral has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Citral in fragrances because of potential sensitization.

More safety Information:
Link to FDA Code of Federal Regulations for Citral:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.60&SearchTerm=citral

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an Acceptable Daily Intake of up to 0.5 mg/kg body weight Citral when used as a flavoring agent.

Link to the JECFA safety evaluation of Citral: http://www.inchem.org/documents/jecfa/jeceval/jec_432.htm

The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Citral and determined that it is Generally Recognized as Safe (GRAS) for use as a flavoring substance. In Europe, Citral is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Citral must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1003432.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 38 - Irritating to skin.* *R 43 - May cause sensitisation by skin contact.* S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Citronellyl Nitrile (*3,7-Dimethyloct-6-enenitrile*)		Y	http://www.thegoodscentscompany.com/data/rw1008932.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Citrus Aurantifolia (Lime) Oil	Y		https://chem.nlm.nih.gov/chemidplus/rn/8008-26-2 *Skin/eye irritant (Lime Oil)* https://chem.nlm.nih.gov/chemidplus/rn/90063-52-8 (Citrus Aurantifolia Extract)
Commiphora Myrrha Oil		Y	http://www.thegoodscentscompany.com/data/es1002061.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/38 - Irritating to skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Commiphora Myrrha Resin	Y		http://www.thegoodscentscompany.com/data/rs1008771.html European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.*
Coriandrum Sativum (Coriander) Fruit Oil (*Cilantro*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/8008-52-4 *Skin/eye irritant* https://www.ewg.org/guides/substances/1504-CORIANDRUMSATIVUMCORIANDEROIL#.W37RTehKiUk Component: LINALOOL Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive Component: LINALOOL

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: GERANIOL Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive Component: GERANIOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Mihály Matura, Birgitta Gruvberger, Magnus Bruze & Ann-Therese Karlberg. 2010. Linalool--a significant contact sensitizer after air exposure. Contact dermatitis 62(1), 32-41. Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Pia Forsström, Ann-Marie Wennberg, Ann-Therese Karlberg & Mihály Matura. 2009. Air oxidation increases skin irritation from fragrance terpenes. Contact dermatitis 60(1), 32-40. Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Deirdre A. Buckley. 2011. Allergy to oxidized linalool in the UK. Contact dermatitis 64(4), 240-1. Component: LINALOOL This peer-reviewed study reports this substance is a contact skin allergen. Mihály Matura, Ian R. White, Cecilia Svedman, Jeanne D. Johansen, An Goossens, Peter Frosch, Magnus Bruze, Klaus E. Andersen, Anna Börje, Maria Sköld & Ann-Therese Karlberg. 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact dermatitis 52(6), 320-8. Component: D-LIMONENE Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/es1003771.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *R 43 - May cause sensitisation by skin contact.*
Coumarin	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/323#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (90.48%): May cause an allergic skin reaction [Warning Sensitization, Skin]* NIOSH Toxicity Data

Ingredient List – Johnson's Baby Powder & Shower-to-Shower

Chemical	Baby Powder	Shower-to-Shower	
			(see below)

Measurement	System	Route/Organism	Dose	Effect	Date
Skin and Eye Irritation		skin /human	5%/2D		June 2017
Skin and Eye Irritation		skin /man	5%		June 2017

Skin Symptoms
MAY BE ABSORBED! Redness. Pain.
from ILO-ICSC

https://www.ewg.org/guides/substances/1528-COUMARIN#.W37OeehKiUk
Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive

The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive

http://www.thegoodscentscompany.com/data/rw1003832.html#tosafty
European information :
Most important hazard(s):
Xn - Harmful.
R 43 - May cause sensitisation by skin contact.
S 24/25 - Avoid contact with skin and eyes.

https://cosmeticsinfo.org/ingredient/coumarin-0
The Food and Drug Administration (FDA) does not permit Coumarin to be directly added to food. The safety of Coumarin has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Coumarin in fragrances because of potential sensitization.

In 2008, the International Fragrance Association (IFRA) issued a position statement that states that the fragrance industry is not aware of any reported systemic adverse health effects with regard to topically applied Coumarin.

More safety Information:
Link to the FDA Code of Federal Regulations for Coumarin:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=189.130&SearchTerm=coumarin

In Europe, Coumarin is included on the list of "allergenic" substances. The European Cosmetics Directive requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic"� substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Coumarin must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin

Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The European Commission's Scientific Committee on Consumer Products (SCCP) evaluated Coumarin as a fragrance allergen and concluded that this ingredient was frequently reported and a well-recognized consumer allergen. Link to the European Commission's SCCP opinion concerning Coumarin: http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out98_en.pdf Coumarin was evaluated by IARC and was not classifiable as to its carcinogenicity in humans. Link to the IARC monograph for Coumarin: https://monographs.iarc.fr/wp-content/uploads/2018/06/mono77-9.pdf https://monographs.iarc.fr/preamble-to-the-iarc-monographs-amended-january-2006/preamble-to-the-iarc-monographs-13/
Cuminum Cyminum (Cumin) Seed Oil (*Cumin Oil*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/8014-13-9 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/es1016101.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.*
Cyclamen Aldehyde	Y	Y	https://chem.nlm.nih.gov/chemidplus/rn/startswith/103-95-7 *Skin/eye irritant* https://www.ewg.org/guides/substances/1563-CYCLAMENALDEHYDE#.W37KcehKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance lacks data on contact allergy in humans. Opinion on Frangrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1004112.html European information : Most important hazard(s): *Xi N - Irritant, Dangerous for the environment.* *R 38 - Irritating to skin.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Decanal	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8175#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (25.17%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard *On direct contact can produce eye and skin irritation;* low general toxicity. (USCG, 1999) from CAMEO Chemicals https://chem.nlm.nih.gov/chemidplus/rn/startswith/112-31-2 Skin/eye irritant https://www.ewg.org/guides/substances/1689-DECANAL#.W37It-hKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance lacks data on contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>http://www.thegoodscentscompany.com/data/rw1000172.html#tosafty
European information :
Most important hazard(s):
Xi N - Irritant, Dangerous for the environment.
R 38 - Irritating to skin.

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>Diethyl Phthalate</td><td></td><td>Y</td><td>https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR758.pdf
https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PRN475.pdf
https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr200.pdf

https://pubchem.ncbi.nlm.nih.gov/compound/6781#section=Hazards-Identification
Signal: Danger
GHS Hazard Statements
H315 (22.62%): Causes skin irritation [Warning Skin corrosion/irritation]

Skin, Eye, and Respiratory Irritations
DEP is slightly irritating to the eye and skin.
Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. V6 824
from HSDB

NIOSH Toxicity Data
<table><tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr><tr><td>Skin and Eye Irritation</td><td></td><td>eye /rabbit</td><td>112 mg</td><td></td><td>October 2017</td></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /human</td><td>2%/3W- intermittent</td><td>mild</td><td>October 2017</td></tr></table>
https://chem.nlm.nih.gov/chemidplus/rn/startswith/84-66-2
Skin/eye irritant

https://cosmeticsinfo.org/ingredient/dimethyl-phthalate-diethyl-phthalate-and-dibutyl-phthalate-0
More safety Information:
The U.S. Food and Drug Administration(FDA) has stated that, at the present time, it does not have evidence that phthalates as used in cosmetics pose a safety risk. FDA noted that an expert panel convened from 1998 to 2000 by the National Toxicology Program (NTP), headquartered at the National Institute of Environmental Health Sciences (NIEHS), concluded that reproductive risks from exposure to phthalates from all sources were minimal to negligible in most cases.

FDA has reviewed all of the available safety and toxicity data for phthalates, including biomonitoring data from the Centers for Disease Control (CDC) measuring levels in human urine, as well as the CIR conclusions based on reviews in 1985 and 2002. None of the data reviewed by FDA established an association between the use of phthalates in cosmetic products and a health risk.</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Based on this information, FDA determined that there wasn't a sound, scientific basis to support taking regulatory action against cosmetics containing phthalates. https://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm128250.htm FDA includes Dimethyl Phthalate (DMP), Diethyl Phthalate (DEP) and Dibutyl phthalate (DBP) on its list of indirect food additives. For example, all three ingredients may be used in adhesives that contact food, DEP and DBP may be used in food contact polymers, and DBP may be used as a slimicide in paper and paperboard used for food packaging. DMP and DEP may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union . DBP is not permitted for use in cosmetics and personal care products in the European Union (see Annex II). DBP was banned in Europe because all substances classified as carcinogenic, mutagenic or toxic to reproduction (categories 1 and 2) under EU chemical hazard classification legislation are automatically banned from use in cosmetics and personal care products, regardless of use concentration. The low exposure to DBP in cosmetics and personal care products was not considered when this ban went into effect. As mentioned earlier, the CIR Expert Panel estimated that exposure to DBP from using cosmetic and personal care products would be well below the dose that did not cause any reproductive and developmental effects in animals. Therefore, the CIR Expert Panel did not see the need to change their original conclusion that DBP was safe as used in cosmetic products. Similar, when considering exposure European experts, (SCCNFP) agree with CIR and concluded in their 2002 opinion that "the safety profile of diethyl phthalate supports its use in cosmetic products at current levels." This opinion was confirmed in a second opinion in 2004. Learn more about EU Cosmetic Regulation: http://ec.europa.eu/growth/tools-databases/cosing/ Learn more about SCCNFP's 2004 opinion on Dibutyl phthalate: http://ec.europa.eu/health/ph_risk/committees/sccp/documents/out287_en.pdf It's a myth that phthalates are 'hidden' in fragrances Fragrances are usually composed of numerous individual substances that are blended together to achieve the desired scent. If a cosmetic product contains a fragrance, this is labelled using the word 'fragrance' or 'parfum' in the ingredients list rather than having to list out all of the individual components. This is legally allowed by the strict cosmetic safety laws and is common practice around the world. It is, however, not a way of 'hiding' ingredients as is sometimes, wrongly, claimed. All of the ingredients that make up the fragrance are still assessed very carefully as part of the overall product safety assessment. DEP and DMP may legally and safely be used as part of the fragrance mix. No substances banned from use as cosmetic ingredients are allowed to be used as components of cosmetic fragrances. Can phthalates be used in personal care products intended for use by children? Phthalate ingredients can be used in personal care products intended for use by children - e.g., in lotions, shampoos, etc. Like personal care products intended for use by adults, the only phthalate that is sometimes present in personal care products intended for children and infants is DEP. The safety of DEP is well accepted among the scientific community. To date, all scientific reviews around the world by key scientific experts and governmental agencies have concluded that DEP is safe for use in cosmetics and personal care products under the current conditions of use. DEP has been reviewed by the U.S. Cosmetic Ingredient Review (CIR) Expert Panel and the European Commission's independent scientific expert committee (the Scientific Committee on Consumer Safety, SCCS and formerly known as the

<table>
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<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>SCCNFP). Both expert scientific groups have approved the safe use of DEP in cosmetic products and have not deemed it necessary to impose any specific warnings or restrictions for its use.

http://www.thegoodscentscompany.com/data/rw1004351.html#tosafty
European information :
Most important hazard(s):
Xn - Harmful.
R 36/37/38 - Irritating to eyes, respiratory system, and skin.</td></tr>
<tr><td>Dihydrocitronellol

(3,7-Dimethyloctan-1-ol)</td><td></td><td>Y</td><td>https://pubchem.ncbi.nlm.nih.gov/compound/7792#section=GHS-Classification
Signal: Warning
GHS Hazard Statements

H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]

https://chem.nlm.nih.gov/chemidplus/rn/startswith/106-21-8
Skin/eye irritant

http://www.thegoodscentscompany.com/data/rw1000592.html#tosafty
European information :
Most important hazard(s):
Xi N - Irritant, Dangerous for the environment.
R 36/38 - Irritating to skin and eyes.

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>Dimethylhydroquinone

(1,4-Dimethoxybenzene)</td><td>Y</td><td></td><td>https://chem.nlm.nih.gov/chemidplus/rn/startswith/150-78-7
Skin/eye irritant

https://pubchem.ncbi.nlm.nih.gov/compound/9016#section=GHS-Classification
Signal: Warning
GHS Hazard Statements

H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]

NIOSH Toxicity Data
<table><tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /guinea pig</td><td>40%/24H</td><td>moderate</td><td>April 2015</td></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>6 gm/12D- intermittent</td><td>mild</td><td>April 2015</td></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>500 mg/24H</td><td>moderate</td><td>April 2015</td></tr></table>
http://www.thegoodscentscompany.com/data/rw1004451.html#tosafty</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Ethyl 3-methyl-3-phenyloxirane-2-carboxylate (*Ethyl Methylphenylglycidate*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/6501#section=Hazards-Identification Signal: Warning GHS Hazard Statements *H317 (77.27%): May cause an allergic skin reaction [Warning Sensitization, Skin]* http://www.thegoodscentscompany.com/data/rw1001602.html#tosafty European information : GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Ethyl Benzoate	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr578.pdf https://pubchem.ncbi.nlm.nih.gov/compound/7165#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (72.29%): Causes skin irritation [Warning Skin corrosion/irritation]* https://cosmeticsinfo.org/ingredient/ethyl-benzoate The Food and Drug Administration (FDA) permits Methyl Benzoate, Ethyl Benzoate, Propyl Benzoate, Isopropyl Benzoate and Isobutyl Benzoate to be used as flavoring agents for direct addition to food. Butyl Benzoate is permitted for use as an indirect food additive as a component of adhesives. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=benzyl%20benzoate https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=175.105 The European Union lists salts and esters of benzoic acid (including Methyl Benzoate, Ethyl Benzoate, Propyl Benzoate, Butyl Benzoate, Isopropyl Benzoate and Isobutyl Benzoate) as preservatives that may be safety used in cosmetics at concentrations up to 0.5% (See Annex IV). Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1004771.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Ethyl heptoate	Y		http://www.thegoodscentscompany.com/data/rw1009172.html#tosafty European information : Most important hazard(s):

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Xi - Irritant *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Ethyl Vanillin	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8467#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (14.69%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard ACUTE/CHRONIC HAZARDS: Toxic. May cause irritation on contact. (NTP, 1992) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations *A human skin irritant.* Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 1610 from HSDB Toxicity Summary HUMAN EXPOSURE AND TOXICITY: Research in humans showed that ethyl vanillin had no significant effect on the activity of five human CYP450 enzymes with concentration ranged from 8 to 128 uM. A 2% concentration of ethyl vanillin caused mild irritation on the skin of humans after 48 hours of direct contact. ANIMAL STUDIES from HSDB https://chem.nlm.nih.gov/chemidplus/rn/startswith/121-32-4 Skin/eye irritant https://www.ewg.org/guides/substances/2100-ETHYLVANILLIN#.W33GAehKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance shows some evidence of causing contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1002652.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* S 24/25 - Avoid contact with skin and eyes. GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Eugenol	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/3314#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (99.88%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			SYMPTOMS: *This compound is a primary irritant and sensitizer and can cause contact dermatitis. Irritation of the skin, eyes and respiratory tract occurs*. Skin contact may cause an inflammatory reaction on the skin. Prolonged or repeated skin contact may cause allergic dermatitis.. Skin sensitization may also occur. (NTP, 1992) from CAMEO Chemicals https://chem.nlm.nih.gov/chemidplus/rn/startswith/97-53-0 *Skin/eye irritant* https://cosmeticsinfo.org/ingredient/eugenol-0 The Food and Drug Administration (FDA) includes clove and its derivatives, including Eugenol, on its list of substances affirmed as Generally Recognized As Safe (GRAS) as direct food substances. The safety of Eugenol has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Eugenol in fragrances because of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for Eugenol: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1257&SearchTerm=eugenol The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an Acceptable Daily Intake for Eugenol of up to 2.5 mg/kg body weight when used as a flavoring agent. Link to the JECFA safety evaluation of Eugenol: http://www.inchem.org/documents/jecfa/jeceval/jec_841.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Eugenol and determined that it is Generally Recognized as Safe (GRAS) for use as a flavoring agent. In Europe, Eugenol is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Eugenol must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1004992.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *R 42/43 - May cause sensitization by inhalation and skin contact.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin sensitization (Category 1), H317*
Formic acid, phenylmethyl ester (*Benzyl formate*)	Y		http://www.thegoodscentscompany.com/data/rw1012591.html#tosafty European information : Most important hazard(s): Xn - Harmful. R 21/22 - Harmful in contact with skin and if swallowed. S 24 - Avoid contact with skin.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) Acute toxicity, Dermal (Category 3), H311
Gamma-Nonalactone (*5-Pentyloxolan-2-one*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7710#section=Hazards-Identification Signal: Warning GHS Hazard Statements *H315 (50%): Causes skin irritation [Warning Skin corrosion/irritation]* Skin, Eye, and Respiratory Irritations *A skin irritiant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 979 from HSDB https://chem.nlm.nih.gov/chemidplus/rn/startswith/104-61-0 Skin/eye irritant http://www.thegoodscentscompany.com/data/rw1000532.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Gamma-Undecalactone	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/104-67-6 Skin/eye irritant https://pubchem.ncbi.nlm.nih.gov/compound/7714#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (19.3%): Causes skin irritation [Warning Skin corrosion/irritation]* ratio from companies that provide hazard codes. Only hazard codes with percentage values above 10% are shown. http://www.thegoodscentscompany.com/data/rw1000822.html#tosafty GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Geraniol	Y	Y	https://chem.nlm.nih.gov/chemidplus/rn/startswith/106-24-1 Skin/eye irritant https://pubchem.ncbi.nlm.nih.gov/compound/637566#section=Hazards-Identification Signal: Danger GHS Hazard Statements *H315 (98.89%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (99.59%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Skin, Eye, and Respiratory Irritations

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			A severe human skin irritant. Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 1440 from HSDB https://www.ewg.org/guides/substances/2340-GERANIOL#.W32bDehKiUk Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/geraniol-0 The Food and Drug Administration (FDA) includes Geraniol on its lists of flavoring substance considered Generally Recognized As Safe (GRAS). The safety of Geraniol has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Geraniol in fragrances because of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for Geraniol: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.60&SearchTerm=geraniol The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Geraniol does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Geraniol: http://www.inchem.org/documents/jecfa/jeceval/jec_898.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Geraniol and determined that it is Generally Recognized as Safe (GRAS) for use as a flavoring substances. In Europe, Geraniol is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic" substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Geraniol must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1006992.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/38 - Irritating to skin and eyes. *R 43 - May cause sensitisation by skin contact.* *S 24/25 - Avoid contact with skin and eyes..* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Geranyl Acetate	Y		https://pubchem.ncbi.nlm.nih.gov/compound/1549026#section=Safety-and-Hazards Signal: Warning

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			GHS Hazard Statements H315 (15.29%): Causes skin irritation [Warning Skin corrosion/irritation] H317 (15.29%): May cause an allergic skin reaction [Warning Sensitization, Skin] Health Hazard SYMPTOMS: Symptoms of exposure to this compound *include skin and eye irritation*.. ACUTE/CHRONIC HAZARDS: This compound can cause eye damage and skin irritation.. (NTP, 1992) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations In human patch test, geraniol @ 32% concn was severely irritating & geranyl acetate mildly irritating. Motoyoski et al; Cosmet Toiletries 94(8): 41 (1979) from HSDB https://chem.nlm.nih.gov/chemidplus/rn/startswith/105-87-3 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1030092.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Heliotropine (*piperonal*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8438#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (96.36%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard SYMPTOMS: Symptoms of exposure to this compound may include depression of the central nervous system and local irritation. ACUTE/CHRONIC HAZARDS: This compound is an irritant. (NTP, 1992) from CAMEO Chemicals TSCA Test Submissions Piperonal (CAS # 120-57-0) was evaluated for primary dermal irritation. The test substance was applied to the cuff of 8 guinea pigs (sex and strain not indicated) at a dose range of 0.25-1.0 mg/kg. Strong skin irritation was evident at 24 hours with slight to gross edema and slight to severe erythema. At 48 hours, slight to moderate edema and erythema was found with eschar formation and necrotic area over part or all of the patch. At 1-week and 2-week observation, desquamation and alopecia was evident. EASTMAN KODAK CO; Letter From Eastman Kodak Co To USEPA Submitting Enclosed Material Safety Data Sheet and Toxicity Report on Piperonal with Attachments; 10/22/91; EPA Doc No. 86-920000085; Fiche No. OTS0533448 from HSDB

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			https://chem.nlm.nih.gov/chemidplus/rn/startswith/120-57-0 Skin/eye irritant http://www.thegoodscentscompany.com/data/rw1005891.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/37/38 - Irritating to eyes, respiratory system, and skin. *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Hexamethylindanopyran (*Galaxolide*)	Y	Y	*Galaxolide* https://chem.nlm.nih.gov/chemidplus/rn/startswith/1222-05-5 Skin/eye irritant https://www.ewg.org/guides/substances/2-GALAXOLIDE#.W32QNuhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1104661.html#tosafty European information : Most important hazard(s): Xi N - Irritant, Dangerous for the environment. *R 38 - Irritating to skin.* *S 24 - Avoid contact with skin.*
Hexane, 1-methoxy- (*Methyl Hexyl Ether*)		Y	http://www.thegoodscentscompany.com/data/rw1017011.html#tosafty European information : Most important hazard(s): *Xi - Irritant* R 38 - Irritating to skin. *S 24/25 - Avoid contact with skin and eyes.*
Hexyl caproate (*Hexyl Hexanoate*)	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/6378-65-0 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rw1028161.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Hydroxycitronellal	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7888#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin]*

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			https://chem.nlm.nih.gov/chemidplus/rn/startswith/107-75-5 Skin/eye irritant https://cosmeticsinfo.org/ingredient/hydroxycitronellal-0 The Food and Drug Administration (FDA) has approved the use of Hydroxycitronellal as a flavoring agent for direct addition to food. The safety of Hydroxycitronellal has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. The IFRA Standard restricts the use of Hydroxycitronellal in fragrances because of potential sensitization. More safety Information: Link to FDA Code of Federal Regulations for Hydroxycitronellal: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=hydroxycitronellal The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Hydroxycitronellal does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Hydroxycitronellal: http://www.inchem.org/documents/jecfa/jeceval/jec_1076.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of Hydroxycitronellal and determined that it was Generally Recognized as Safe for use as a flavoring substance. In Europe, Hydroxycitronellal is included on the list of "allergenic" substances. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic"� substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Hydroxycitronellal must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1000972.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* *S 24 - Avoid contact with skin.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317*
Isoamyl Acetate	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr469.pdf https://pubchem.ncbi.nlm.nih.gov/compound/31276#section=Safety-and-Hazards Signal: Danger GHS Hazard Statements *H315: Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			VAPOR: Irritating to eyes, nose and throat. If inhaled, will cause nausea, headache or dizziness. LIQUID: Irritating to skin and eyes. Harmful if swallowed. (USCG, 1999) from CAMEO Chemicals https://cosmeticsinfo.org/ingredient/isoamyl-acetate The Food and Drug Administration reviewed the safety of Amyl Acetate and approved its use as an indirect food additive as a component of adhesives. FDA: Link to the Code of Federal Regulations for Amyl Acetate https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=175.105&SearchTerm=amyl%20acetate The use of Amyl Acetate and Isoamyl Acetate are permitted in Europe subject to the general provisions of the Cosmetics Regulation of the European Union. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 The Joint FAO/WHO Expert Committee on Food Additives has established an Acceptable Daily Intake of 0-3 mg Isoamyl Acetate/kg body weight. No safety concern was indicated at current levels of intake when used as a flavoring agent. http://www.inchem.org/documents/jecfa/jeceval/jec_1138.htm http://www.thegoodscentscompany.com/data/rw1006712.html#tosafty European information : Most important hazard(s): Xi - Irritant *R 66 - Repeated exposure may cause skin dryness or cracking.*
Isopropyl Palmitate		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR623.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PRN475.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr238.pdf https://cosmeticsinfo.org/ingredient/isopropyl-palmitate https://chem.nlm.nih.gov/chemidplus/rn/startswith/142-91-6 Skin/eye irritant http://www.thegoodscentscompany.com/data/rw1019311.html#tosafty European information : Most important hazard(s): *S 24/25 - Avoid contact with skin and eyes.* https://pubchem.ncbi.nlm.nih.gov/compound/8907#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]* Skin, Eye, and Respiratory Irritations

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>Direct contact may cause mild irritation /of the/ eye. Prolonged or repeated contact /with the skin/ may cause mild irritation...
European Commission, ESIS; IUCLID Dataset,Isopropyl Palmitate (142-91-6) p.24 (2000 CD-ROM edition).
from HSDB

A human skin irritant.
Lewis, R.J. Sax's Dangerous Properties of Industrial Materials. 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996., p. 1991
from HSDB

NIOSH Toxicity Data

<table>
<tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr>
<tr><td>Skin and Eye Irritation</td><td></td><td>skin /human</td><td>84 mg/3D- intermittent</td><td>mild</td><td>January 1997</td></tr>
<tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>500 mg/24H</td><td>moderate</td><td>January 1997</td></tr>
</table></td></tr>
<tr><td>Juniperus Communis Fruit Oil</td><td>Y</td><td></td><td>https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr328.pdf

https://www.ewg.org/guides/substances/10468-JUNIPERUSCOMMUNISFRUITOIL#.W31_sehKiUk
Component: D-LIMONENE
Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive

https://chem.nlm.nih.gov/chemidplus/number/startswith/8012-91-7
Skin/eye irritant

https://cosmeticsinfo.org/ingredient/juniperus-communis-fruit-extract
The Food and Drug Administration (FDA) includes Juniperus communis berry oil on its list of essential oils considered Generally Recognized As Safe (GRAS) as food for human consumption. Juniper tar is approved for use as an analgesic, anesthetic, and antipruretic active ingredient in Over-The-Counter (OTC) anorectal drug products.

Link to FDA Code of Federal Regulations for Juniper berry oil and Juniper Tar

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.20&SearchTerm=juniperus
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=346.16&SearchTerm=juniper%20tar

Juniper Extracts and Juniper Tar may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union.

Link to the EU Cosmetic Regulation:
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013

http://www.thegoodscentscompany.com/data/es1029741.html
European information :
Most important hazard(s):
R 38 - Irritating to skin.</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			R 43 - May cause sensitisation by skin contact. *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Lavandula Angustifolia (Lavender) Oil	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/8000-28-0 Skin/eye irritant https://www.ewg.org/guides/substances/3172-LAVANDULAANGUSTIFOLIALAVENDER#.W319L-hKiUk Component: LINALOOL Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive Component: LINALOOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALYL ACETATE The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: GERANIOL Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive Component: GERANIOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Mihály Matura, Birgitta Gruvberger, Magnus Bruze & Ann-Therese Karlberg. 2010. Linalool--a significant contact sensitizer after air exposure. Contact dermatitis 62(1), 32-41. Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Pia Forsström, Ann-Marie Wennberg, Ann-Therese Karlberg & Mihály Matura. 2009. Air oxidation increases skin irritation from fragrance terpenes. Contact dermatitis 60(1), 32-40. Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Deirdre A. Buckley. 2011. Allergy to oxidized linalool in the UK. Contact dermatitis 64(4), 240-1. Component: LINALOOL This peer-reviewed study reports this substance is a contact skin allergen. Mihály Matura, Ian R. White, Cecilia Svedman, Jeanne D. Johansen, An Goossens, Peter Frosch, Magnus Bruze, Klaus E. Andersen, Anna Börje, Maria Sköld & Ann-Therese Karlberg. 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact dermatitis 52(6), 320-8. http://www.thegoodscentscompany.com/data/es1007471.html#tosafty

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			European information : Most important hazard(s): *Xn - Harmful.* *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* *S 24/25 - Avoid contact with skin and eyes.*
Lemon oil terpenes	Y		https://echa.europa.eu/substance-information/-/substanceinfo/100.108.674 Danger! According to the classification provided by companies to ECHA in CLP notifications this substance may be fatal if swallowed and enters airways, is very toxic to aquatic life with long lasting effects, is very toxic to aquatic life, is a flammable liquid and vapour, *causes skin irritation and may cause an allergic skin reaction.*
Levisticum Officinale Oil (*Levisticum Officinale Leaf Oil*)		Y	https://chem.nlm.nih.gov/chemidplus/rn/startswith/8016-31-7 *Skin/eye irritant*
Linalool	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/78-70-6 *Skin/eye irritant* https://www.ewg.org/guides/substances/3258-LINALOOL#.W312eOhKiUk Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Mihály Matura, Birgitta Gruvberger, Magnus Bruze & Ann-Therese Karlberg. 2010. Linalool--a significant contact sensitizer after air exposure. Contact dermatitis 62(1), 32-41. This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Pia Forsström, Ann-Marie Wennberg, Ann-Therese Karlberg & Mihály Matura. 2009. Air oxidation increases skin irritation from fragrance terpenes. Contact dermatitis 60(1), 32-40. This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Deirdre A. Buckley. 2011. Allergy to oxidized linalool in the UK. Contact dermatitis 64(4), 240-1. This peer-reviewed study reports this substance is a contact skin allergen. Mihály Matura, Ian R. White, Cecilia Svedman, Jeanne D. Johansen, An Goossens, Peter Frosch, Magnus Bruze, Klaus E. Andersen, Anna Börje, Maria Sköld & Ann-Therese Karlberg. 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact dermatitis 52(6), 320-8. https://cosmeticsinfo.org/ingredient/linalool-0 The Food and Drug Administration (FDA) includes Linalool on its list of substances considered Generally Recognized As Safe (GRAS) as flavoring substance. The safety of Linalool has been evaluated by the Research Institute for Fragrance Materials Expert Panel (REXPAN). Based on this evaluation, an International Fragrance Association (IFRA) Standard has been established. *The IFRA Standard restricts the use of Linalool in fragrances because of potential sensitization.* More safety Information: Link to FDA Code of Federal Regulations for Linalool: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=182.60&SearchTerm=linalool

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that Linalool does not present a safety concern at current levels of intake when used as a flavoring agent. Link to the JECFA safety evaluation of Linalool: http://www.inchem.org/documents/jecfa/jeceval/jec_1271.htm The Flavor and Extract Manufacturers Association Expert Panel has reviewed the safety of linalool and determined that it is Generally Recognized as Safe (GRAS) for use as a flavoring substance. *In Europe, Linalool is included on the list of "allergenic"� substances*. The European Cosmetics Regulation requires manufacturers of cosmetics and personal care products to indicate the presence of certain "allergenic"� substances in the list of ingredients if they are present above certain levels in the product (see Annex III). The presence of Linalool must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on the skin products 0.01% in products that are rinsed off the skin Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1007872.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* https://pubchem.ncbi.nlm.nih.gov/compound/6549#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (96.96%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (53.26%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Skin, Eye, and Respiratory Irritations *A skin irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2232 from HSDB ... *Linalool must be regarded as a skin irritant and should be seen as mildly irritant for man*. ... Linalool is at most a moderate eye irritant; moreover, in about a third of human subjects it did not cause any eye irritation at 320 ppm. Organization for Economic Cooperation and Development; Screening Information Data Set for LINALOOL (78-70-6) p.14 (March 2002). from HSDB NIOSH Toxicity Data https://pubchem.ncbi.nlm.nih.gov/compound/6549#section=NIOSH-Toxicity-Data&fullscreen=true

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><th>Measurement</th><th>Date</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>eye /rabbit</td><td>100 µL</td><td>moderate</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>eye /rabbit</td><td>0.1 mL/1H</td><td>moderate</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /guinea pig</td><td>100 mg/24H</td><td>moderate</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /human</td><td>32%/72H</td><td>mild</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /human</td><td>10%/2D</td><td></td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /man</td><td>16 mg/48H</td><td>mild</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /rabbit</td><td>500 mg/24H</td><td>mild</td></tr>
<tr><td>Skin and Eye Irritation</td><td>October 2017</td><td></td><td>skin /rabbit</td><td>100 mg/24H</td><td>severe</td></tr>
</table>
</td></tr>
<tr><td>Linalyl Acetate</td><td>Y</td><td></td><td>
https://pubchem.ncbi.nlm.nih.gov/compound/8294#section=Safety-and-Hazards
Signal: Warning
GHS Hazard Statements

H315 (98.36%): Causes skin irritation [Warning Skin corrosion/irritation]

Skin, Eye, and Respiratory Irritations
A severe skin irritant.
Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2232
from HSDB

Linalyl acetate (100%) appeared to be severely irritating to rabbit skin and moderately irritating to the skin of the guinea pig. In a test with miniature swines, application of 0.05 g linalyl acetate under a patch for 48 hours /caused/ no irritation ... .
Organization for Economic Cooperation and Development; Screening Information Data Set for LINALYL ACETATE (115-95-7) p.11 (March 2002). Available from, as of July 14, 2008: http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html
from HSDB

https://chem.nlm.nih.gov/chemidplus/rn/startswith/115-95-7
Skin/eye irritant

https://www.ewg.org/guides/substances/3259-LINALYLACETATE#.W31y2-hKiUk
The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans.

Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive
</td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			http://www.thegoodscentscompany.com/data/rw1007892.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Mentha Arvensis Leaf Oil	Y		http://www.thegoodscentscompany.com/data/es1003041.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 37/38 - Irritating to respiratory system and skin.* https://www.ewg.org/guides/substances/6437-MENTHAARVENSISWILDMINTOIL#.W31vDuhKiUk Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Mihály Matura, Birgitta Gruvberger, Magnus Bruze & Ann-Therese Karlberg. 2010. Linalool--a significant contact sensitizer after air exposure. Contact dermatitis 62(1), 32-41. Johanna Bråred Christensson, Pia Forsström, Ann-Marie Wennberg, Ann-Therese Karlberg & Mihály Matura. 2009. Air oxidation increases skin irritation from fragrance terpenes. Contact dermatitis 60(1), 32-40. Deirdre A. Buckley. 2011. Allergy to oxidized linalool in the UK. Contact dermatitis 64(4), 240-1. Component: LINALOOL This peer-reviewed study reports this substance is a contact skin allergen. Mihály Matura, Ian R. White, Cecilia Svedman, Jeanne D. Johansen, An Goossens, Peter Frosch, Magnus Bruze, Klaus E. Andersen, Anna Börje, Maria Sköld & Ann-Therese Karlberg. 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact dermatitis 52(6), 320-8. The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALOOL Recognized by the European Union as a skin allergen Allergen list - EU Cosmetics Directive Component: LINALOOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive
Menthyl Acetate	Y		http://www.thegoodscentscompany.com/data/rw1046271.html#tosafty European information : Most important hazard(s):

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Xi - Irritant *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.*
Methyl Anthranilate	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8635#section=GHS-Classification Health Hazard SYMPTOMS: *This compound is an irritant to the skin. ACUTE/CHRONIC HAZARDS: This compound may cause irritation on contact*. (NTP, 1992). from CAMEO Chemicals Skin, Eye, and Respiratory Irritations Prolonged inhalation may lead to respiratory tract irritation. ...*Prolonged or repeated /skin or eye/ contact may result in mechanical irritation*. Becker Underwood, Inc; Material Safey Data Sheet for Methyl Anthranilate 134-20-3 (Date Revised: February 23, 2000). Available from, as of November 11, 2003: http://www.beckerunderwood.com/msds/rejexit_ff.html from HSDB https://chem.nlm.nih.gov/chemidplus/rn/startswith/134-20-3 Skin/eye irriatant https://www.ewg.org/guides/substances/11032-METHYLANTHRANILATE#.W3yJwuhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance shows negative results for causing contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1008211.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Methyl Benzoate	Y	Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr578.pdf https://cosmeticsinfo.org/ingredient/methyl-benzoate The Food and Drug Administration (FDA) permits Methyl Benzoate, Ethyl Benzoate, Propyl Benzoate, Isopropyl Benzoate and Isobutyl Benzoate to be used as flavoring agents for direct addition to food. Butyl Benzoate is permitted for use as an indirect food additive as a component of adhesives. Link to FDA Code of Federal Regulations https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=benzyl%20benzoate https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=175.105

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			The European Union lists salts and esters of benzoic acid (including Methyl Benzoate, Ethyl Benzoate, Propyl Benzoate, Butyl Benzoate, Isopropyl Benzoate and Isobutyl Benzoate) as preservatives that may be safety used in cosmetics at concentrations up to 0.5% (See Annex IV). Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 http://www.thegoodscentscompany.com/data/rw1015012.html#tosafty European information : Most important hazard(s): Xn - Harmful. R 36/38 - Irritating to skin and eyes. R 42/43 - May cause sensitization by inhalation and skin contact. S 24/25 - Avoid contact with skin and eyes.
Methyl Cinnamate	Y		https://pubchem.ncbi.nlm.nih.gov/compound/637520#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H317 (100%): May cause an allergic skin reaction [Warning Sensitization, Skin]* https://www.ewg.org/guides/substances/18329-METHYLCINNAMATE#.W3yEyuhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance shows some evidence of causing contact allergy in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive http://www.thegoodscentscompany.com/data/rw1417571.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes.
Methyl Salicylate	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr302.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/TR766.pdf https://chem.nlm.nih.gov/chemidplus/rn/startswith/119-36-8 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/4133#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (23.08%): Causes skin irritation [Warning Skin corrosion/irritation]* Health Hazard *Harmful if swallowed, inhaled, absorbed through skin*. Vapor mist is irritating to the eyes, mucous membranes, upper respiratory tract and skin. Ingestion of relatively small amount causes severe poisoning and death. Causes nausea, vomiting, acidosis, pulmonary edema, pneumonia, convulsions and death. (USCG, 1999) from CAMEO Chemicals Effects of Short Term Exposure *The substance is irritating to the eyes and skin*. The substance may cause effects on the central nervous system. This may result in shock and death. The effects may be delayed. Medical observation is indicated.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			from ILO-ICSC http://www.thegoodscentscompany.com/data/rw1008472.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* https://www.ewg.org/guides/substances/3576-METHYLSALICYLATE#.W3yBzuhKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive https://cosmeticsinfo.org/ingredient/methyl-salicylate The Food and Drug Administration (FDA) has reviewed the safety of Salicylic Acid and Methyl Salicylate and permits their use as indirect food additives. Salicylic Acid is approved for use in Over-the-Counter (OTC) drug products. Salicylic acid is widely used as an FDA approved safe and effective acne drug product. It is also approved for use in OTC drugs for corn, callusand wart removal, as well as in antidandruff OTC drug products. Ethylhexyl Salicylate and TEA-Salicylate are permitted by FDA for use as active ingredients in OTC sunscreen drug products. Ethylhexyl Salicylate may be used at concentrations up to 5%, and TEA-Salicylate may be used at concentrations up to 12%. Link to the FDA Code of Federal Regulations for Salicylic Acid, Sodium Salicylate, Methyl Salicylate, and Octyl (Ethylhexyl) Salicylate Acne Active Ingredients Adhesives Sunscreen Active Ingredients Wart Remover Active Ingredients Corn and Callus Remover Active ingredients Control of Dandruff Salicylic Acid it salts are listed in the Cosmetics Directive of the European Union and may be used as preservatives in cosmetics and personal care products at a maximum concentration of 0.5% (see Annex VI). In Europe, for uses other than as a preservative, Salicylic Acid may be used in rinse-off hair products at concentrations up to 3%, and in other products at concentrations up to 2% (see Annex III). Salicylic Acid should not to be used in products for children under 3 years of age, except for shampoo formulations. Ethylhexyl Salicylate is listed in the Cosmetics Directive of the European Union and may be used as a UV filter at a concentration up to 5% (see Annex VII). Health Canada permits the use of Salicylic Acid in cosmetics and personal care products in concentrations equal to or less than 2%. Ethylhexyl Salicylate (up to 6%) and TEA-Salicylate (up to 12%) are permitted for use in sunscreen products in Canada.
Myristica Fragrans (Nutmeg) Kernel Oil (*Nutmeg oil*)	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/6850746#section=Canonical-SMILES https://chem.nlm.nih.gov/chemidplus/rn/startswith/8008-45-5 *Skin/eye irritant* https://www.ewg.org/guides/substances/3802-MYRISTICAFRAGRANSNUTMEGKERNELOIL#.W3x8BuhKiUk Component: D-LIMONENE Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive Impurity: FORMALDEHYDE

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Causes skin irritation. NIOSH Pocket Guide to Chemical Hazards - Centers for Disease Control and Prevention (CDC)
Myroxylon Balsamum (Balsam Tolu) Resin	Y		https://chem.nlm.nih.gov/chemidplus/rn/startswith/9000-64-0 *Skin/eye irritant* http://www.thegoodscentscompany.com/data/rs1011391.html European information : Most important hazard(s): Xi - Irritant *R 43 - May cause sensitisation by skin contact.*
Myroxylon Pereirae (Balsam Peru) Oil	Y		https://www.ewg.org/skindeep/ingredient/720874/MYROXYLON_PEREIRAE_(BALSAM_PERU)_OIL/#.W3x4b-hKiUk http://www.thegoodscentscompany.com/data/es1009811.html#tosafty European information : Most important hazard(s): Xi - Irritant *R 38 - Irritating to skin.* *R 43 - May cause sensitisation by skin contact.* *S 24/25 - Avoid contact with skin and eyes.* *S 28 - After contact with skin, wash immediately with plenty of water.*
Nonan-1-ol (*Nonyl Alcohol*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/8914#section=Safety-and-Hazards Signal: Warning GHS Hazard Statements *H315 (17.45%): Causes skin irritation [Warning Skin corrosion/irritation]*
Octan-2-one (*2-Octanone*)		Y	https://pubchem.ncbi.nlm.nih.gov/compound/8093#section=Hazards-Identification Skin, Eye, and Respiratory Irritations 2-Octanone has a relatively low toxicity. *Direct skin contact may cause defatting and irritation of the skin.* Bingham, E.; Cohrssen, B.; Powell, C.H.; Patty's Toxicology Volumes 1-9 5th ed. John Wiley & Sons. New York, N.Y. (2001)., p. 6:301. from HSDB http://www.thegoodscentscompany.com/data/rw1001751.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 21 - Harmful in contact with skin.* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *S 24/25 - Avoid contact with skin and eyes.*
Opoponax (*sweet myrrh*)	Y		https://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_025b.pdf According to the results of these tests, summarized in the table, five of the tested samples (2 extracts and 3 oils) gave some positive results indicating that Opoponax products may have a *mild sensitizing potential depending on the origin and the quality of the product.* In the introductory report (ref. 29) it is stated that the earlier studies with positive resu1ts were most likely due to the utilization of samples that contained undefined impurities. The more recent studies yielding negative results used better-defined materials. However, in the same report it is also stated that the source of the samples with positive results is unknown, and may have been obtained from Pastinaca opopanax L. (Fam: Umbelliferare) instead of from genuine opoponax gums from Commiphora erythraea var. glabrescens Engler (Fam: Burseracae). Taking also into consideration that the most recent studies mentioned above were carried out in 1979-1980, these two partially contradicting statements cannot be evaluated.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
p-Cresol	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr277.pdf https://cosmeticsinfo.org/ingredient/p-cresol The Food and Drug Administration (FDA) permits the use of Thymol as a direct and food additive (as a flavoring substance) and as an indirect food additive (for use in paper an paperboard in contact with food). Link to FDA Code of Federal Regulations for Thymol https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=thymol https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=176.180&SearchTerm=thymol In the European Union, p-Chloro-m-Cresol, Sodium p-Chloro-m-Cresol at concentrations up to 0.2% and o-Cymen-5-ol (4-Isopropyl-m-cresol) at concentrations up to 0.1% are allowed to be used as preservatives (see Annex VI). Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 https://chem.nlm.nih.gov/chemidplus/rn/106-44-5 *Skin/eye irritant* Tumor Data http://www.thegoodscentscompany.com/data/rw1003851.html#tosafty European information : Most important hazard(s): T - Toxic. *R 24/25 - Toxic in contact with skin and if swallowed.* R 34 - Causes burns. *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Acute toxicity, Dermal (Category 3), H311* *Skin corrosion (Category 1B), H314* https://pubchem.ncbi.nlm.nih.gov/compound/2879#section=Hazards-Identification Signal: Danger GHS Hazard Statements *H311: Toxic in contact with skin [Danger Acute toxicity, dermal]* *H314: Causes severe skin burns and eye damage [Danger Skin corrosion/irritation]* H351: Suspected of causing cancer [Warning Carcinogenicity] Health Hazard *SKIN: Intense burning, loss of feeling, white discoloration and softening.* Gangrene may occur. (USCG, 1999) from CAMEO Chemicals Skin, Eye, and Respiratory Irritations

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			... Causes severe eye and skin burns. ... Irritating to skin, eyes, and respiratory system. Symptoms include severe irritation of eyes with tearing, conjunctivitis, and corneal edema. *May act as a skin sensitizer.* National Fire Protection Association; Fire Protection Guide to Hazardous Materials. 14TH Edition, Quincy, MA 2010, p. 49-48 from HSDB NIOSH Toxicity Data Tumorigenic Data — June 2017 — skin/mouse — lowest published toxic dose: 2280 mg/kg/20W-intermittent — Tumorigenic: Neoplastic by RTECS criteria; Skin and Appendages: Tumors
p-Cymene	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7463#section=Hazards-Identification *p-Cymene is reported to be a primary skin irritant ... .* Monograph on Fragrance Raw Materials: p-Cymene; Food and Cosmetics Toxicology 12 (3): 401-2 (1974) from HSDB http://www.thegoodscentscompany.com/data/rw1032712.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 36/37/38 - Irritating to eyes, respiratory system, and skin..* *S 24/25 - Avoid contact with skin and eyes..* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315*
Pelargonium Graveolens Flower Oil *(Geranium)*	Y		https://www.ewg.org/guides/substances/4320-PELARGONIUMGRAVEOLENSGERANIUMEXTRACT#.W3xhjehKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance is an established *contact allergen* in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Directive Component: GERANIOL Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive Component: GERANIOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALOOL Recognized by the European Union as a skin allergen. Allergen list - EU Cosmetics Directive. Component: LINALOOL The European Commission's Scientific Committee on Consumer Safety reports this substance is an established contact allergen in humans. Opinion on Fragrance allergens in cosmetics (2011) - EU Cosmetics Directive Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Johanna Bråred Christensson, Mihály Matura, Birgitta Gruvberger, Magnus Bruze & Ann-Therese Karlberg. 2010. Linalool--a significant contact sensitizer after air exposure. Contact dermatitis 62(1), 32-41.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Component: LINALOOL This peer-reviewed study reports this substance is a significant skin sensitizer after oxidation. Deirdre A. Buckley. 2011. Allergy to oxidized linalool in the UK. Contact dermatitis 64(4), 240-1. Component: LINALOOL This peer-reviewed study reports this substance is a contact skin allergen. Mihály Matura, Ian R. White, Cecilia Svedman, Jeanne D. Johansen, An Goossens, Peter Frosch, Magnus Bruze, Klaus E. Andersen, Anna Börje, Maria Sköld & Ann-Therese Karlberg. 2005. Selected oxidized fragrance terpenes are common contact allergens. Contact dermatitis 52(6), 320-8. https://pubchem.ncbi.nlm.nih.gov/compound/637566#section=GHS-Classification (Geraniol): Signal: Danger GHS Hazard Statements *H315 (98.89%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (99.59%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Skin, Eye, and Respiratory Irritations *A severe human skin irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 1440. from HSDB
Pentadecalactone (*omega-pentadecalactone*) (*Oxacyclohexadecan-2-one*)	Y		https://pubchem.ncbi.nlm.nih.gov/compound/235414#section=GHS-Classification Signal: Warning GHS Hazard Statements *H317 (18.4%): May cause an allergic skin reaction [Warning Sensitization, Skin]* http://www.thegoodscentscompany.com/data/rw1004211.html#tosafty European information : Most important hazard(s): *S 24/25 - Avoid contact with skin and eyes.*
Petitgrain oil, Paraguay (*Citrus aurantium fruit oil*)	Y		https://echa.europa.eu/substance-information/-/substanceinfo/100.252.174 Essential oil of Petitgrain obtained from the leaves and twigs of Citrus aurantium (Rutaceae) by distillation Danger! According to the classification provided by companies to ECHA in REACH registrations this substance may be fatal if swallowed and enters airways, is toxic to aquatic life with long lasting effects, causes serious eye irritation and *causes skin irritation.*
Phenethyl Acetate	Y		https://pubchem.ncbi.nlm.nih.gov/compound/7654#section=Hazards-Identification Signal: Danger GHS Hazard Statements http://www.thegoodscentscompany.com/data/rw1010032.html#tosafty European information : Most important hazard(s): *S 24/25 - Avoid contact with skin and eyes.*
Phenethyl Alcohol	Y	Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr134.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/prn547.PDF

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			http://www.thegoodscentscompany.com/data/rw1010052.html#tosafty European information : Most important hazard(s): Xn - Harmful. *R 21/22 - Harmful in contact with skin and if swallowed.* *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.* https://cosmeticsinfo.org/ingredient/phenethyl-alcohol-0 More safety Information: Link to FDA Code of Federal Regulations for Phenethyl Alcohol https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=172.515&SearchTerm=phenethyl%20alcoho Phenethyl Alcohol may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 https://www.ewg.org/guides/substances/4400-PHENETHYLALCOHOL#.W3xBDehKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance shows some evidence of causing *contact allergy in humans*. Opinion on Fragrance allergens in cosmetics (2011) – EU Cosmetics Directive https://pubchem.ncbi.nlm.nih.gov/compound/6054#section=GHS-Classification Signal: Warning Effects of Short Term Exposure *The substance is irritating to the eyes, skin and respiratory tract*. The substance may cause effects on the central nervous system. If swallowed the substance may cause vomiting and could result in aspiration pneumonitis. from ILO-ICSC* Effects of Long Term Exposure Animal tests show that this substance possibly causes toxicity to human reproduction or development. from ILO-ICSC* Skin Symptoms Redness. from ILO-ICSC* ** The International Chemical Safety Cards (ICSC) are data sheets intended to provide essential safety and health information on chemicals in a clear and concise way. The primary aim of the cards is to promote the safe use of chemicals in the workplace.* https://pubchem.ncbi.nlm.nih.gov/compound/6054#section=Toxicity From NIOSH

Skin and Eye Irritation		eye /rabbit	12 gm/10M	mild	July 2016

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			Skin and Eye Irritation · eye /rabbit · 750 µg/24H · severe · July 2016 Skin and Eye Irritation · skin /guinea pig · 100% · mild · July 2016 Skin and Eye Irritation · skin /guinea pig · 100 mg/24H · moderate · July 2016 Skin and Eye Irritation · skin /rabbit · 100 mg/24H · moderate · July 2016
Phenethyl Benzoate	Y		http://www.thegoodscentscompany.com/data/rw1012671.html#tosafty European information : Most important hazard(s): Xi - Irritant *R 36/38 - Irritating to skin and eyes.* *S 24/25 - Avoid contact with skin and eyes.*
Phenoxyethanol	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr139.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR609.pdf https://cosmeticsinfo.org/ingredient/phenoxyethanol-0 European Union (E.U.) Regulation (EC) No. 1223/2009 of the European Union lists phenoxyethanol in Annex V, the list of preservatives allowed in cosmetic products. The maximum concentration in ready for use concentrations is 1.0%. https://chem.nlm.nih.gov/chemidplus/rn/122-99-6 *Skin/eye irritant* https://pubchem.ncbi.nlm.nih.gov/compound/31236#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (75.94%): Causes skin irritation [Warning Skin corrosion/irritation]* *A skin and severe eye irritant.* Lewis, R.J. Sr. (ed) Sax's Dangerous Properties of Industrial Materials. 11th Edition. Wiley-Interscience, Wiley & Sons, Inc. Hoboken, NJ. 2004., p. 2904 from HSDB
phenylacetaldehyde	Y		https://www.ewg.org/guides/substances/16215-PHENYLACETALDEHYDE#.W3w8T-hKiUk The European Commission's Scientific Committee on Consumer Safety reports this substance shows some evidence of causing contact allergy in humans Opinion on Fragrance allergens in cosmetics (2011) EU Cosmetics Directive https://pubchem.ncbi.nlm.nih.gov/compound/998#section=GHS-Classification Signal: Danger

<table>
<tr><th colspan="4">Ingredient List – Johnson's Baby Powder & Shower-to-Shower</th></tr>
<tr><th>Chemical</th><th>Baby Powder</th><th>Shower-to-Shower</th><th></th></tr>
<tr><td></td><td></td><td></td><td>GHS Hazard Statements
H314 (74.67%): Causes severe skin burns and eye damage [Danger Skin corrosion/irritation]
H317 (96.46%): May cause an allergic skin reaction [Warning Sensitization, Skin]

http://www.thegoodscentscompany.com/data/rw1009931.html#tosafty
European information :
Most important hazard(s):
Xn - Harmful
R 36/37/38 - Irritating to eyes, respiratory system, and skin.
R 43 - May cause sensitisation by skin contact.

GHS Classification in accordance with 29 CFR 1910 (OSHA HCS)
Skin irritation (Category 2), H315</td></tr>
<tr><td>p-Methyl Acetophenone</td><td>Y</td><td></td><td>https://chem.nlm.nih.gov/chemidplus/rn/122-00-9
Skin/eye irritant

https://pubchem.ncbi.nlm.nih.gov/compound/8500#section=GHS-Classification
Signal: Warning
GHS Hazard Statements
H315 (79.94%): Causes skin irritation [Warning Skin corrosion/irritation]

http://www.thegoodscentscompany.com/data/rw1008191.html#tosafty
European information :
Most important hazard(s):
Xn - Harmful.
R 22 - Harmful if swallowd.
R 36/38 - Irritating to skin and eyes.
S 24/25 - Avoid contact with skin and eyes.</td></tr>
<tr><td>Pogostemon Cablin Oil

(Patchouli)</td><td>Y</td><td>Y</td><td>https://chem.nlm.nih.gov/chemidplus/rn/8014-09-3
Skin/eye irritant

http://www.thegoodscentscompany.com/data/es1031631.html#tosafty
European information :
Most important hazard(s):
Xi - Irritant
R 36/38 - Irritating to skin and eyes.
S 24/25 - Avoid contact with skin and eyes.

Signal word Warning
Hazard statement(s)
H316 - Causes mild skin irritation</td></tr>
<tr><td>Propanedioic acid, diethyl ester

(Diethyl Malonate)</td><td>Y</td><td></td><td>https://pubchem.ncbi.nlm.nih.gov/compound/7761#section=Toxicity
<table><tr><th>Measurement</th><th>System</th><th>Route/Organism</th><th>Dose</th><th>Effect</th><th>Date</th></tr><tr><td>Skin and Eye Irritation</td><td></td><td>skin /rabbit</td><td>500 mg/24H</td><td>mild</td><td>January 1997</td></tr></table></td></tr>
</table>

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
Propanoic acid, phenylmethyl ester *(Benzyl Propionate)*	Y	Y	http://www.thegoodscentscompany.com/data/rw1001772.html#tosafty European information : Most important hazard(s): *S 24/25 - Avoid contact with skin and eyes.* Signal word Warning
Propylene Glycol		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR560.PDF https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr77.pdf https://cosmeticsinfo.org/ingredient/propylene-glycol Safety Information: United States FDA: The agency includes propylene glycol on its list of substances considered Generally Recognized As Safe (GRAS) for direct addition to food. Polypropylene glycol is also permitted as an indirect food additive for use as a de-foaming agent. NTP: In 2003, the National Toxicology Program's (NTP) Center for the Evaluation of Risk to Human Reproduction (CERHR) Expert Panel reviewed the reproductive and developmental effects potential of propylene glycol and concluded that there is "negligible concern for reproductive or developmental toxicity to humans." European Union (EU) Propylene glycol and PPGs may be used in cosmetics and personal care products marketed in Europe according to the general provisions of the Cosmetics Regulation of the European Union. https://www.ewg.org/guides/substances/4889-PROPYLENEGLYCOL#.W3wnlehKiUk The OECD concluded that *Propylene Glycol does not cause sensitization by skin contact*. Organisation for Economic Co-Operation and Development. 2001. Propylene glycol CAS No. 57-55-6. SIDS Initial Assessment Report for 11th SIAM. The OECD concluded that *Propylene Glycol is not a skin irritant*. Organisation for Economic Co-Operation and Development. 2001. Propylene glycol CAS No. 57-55-6. SIDS Initial Assessment Report for 11th SIAM. The Agency for Toxic Substances and Disease Registry concluded that *Propylene Glycol has marginal irritant properties*. U.S. Department of Health and Human Services - Agency for Toxic Substances and Disease Registry. 1997. Toxicological Profile For Propylene Glycol. The Agency for Toxic Substances and Disease Registry found cases of sensitivity recorded in the *Propylene Glycol literature and concluded that it might be a sensitizer*. U.S. Department of Health and Human Services - Agency for Toxic Substances and Disease Registry. 1997. Toxicological Profile For Propylene Glycol. https://pubchem.ncbi.nlm.nih.gov/compound/1030#section=NIOSH-Toxicity-Data&fullscreen=true

Skin and Eye Irritation	June 2017		eye /rabbit	100 mg	mild
Skin and Eye Irritation	June 2017		eye /rabbit	500 mg/24H	mild

Ingredient List – Johnson's Baby Powder & Shower-to-Shower

Chemical	Baby Powder	Shower-to-Shower						
			Skin and Eye Irritation	June 2017		skin /child	30%/96H-continuous	moderate
			Skin and Eye Irritation	June 2017		skin /human	500 mg/7D	mild
			Skin and Eye Irritation	June 2017		skin /human	104 mg/3D- intermittent	moderate
			Skin and Eye Irritation	June 2017		skin /human	20%	
			Skin and Eye Irritation	June 2017		skin /man	10%/2D	
			Skin and Eye Irritation	June 2017		skin /woman	30%/96H open irritation test	mild
			Mutation Data	June 2017	Cytogenetic Analysis	subcutaneous/mouse	8000 mg/kg	
			Mutation Data	June 2017	Cytogenetic Analysis	fibroblast/hamster	32 gm/L	
Santalum Album (Sandalwood) Oil	Y		http://www.thegoodscentscompany.com/data/es1010871.html#tosafty European information : Most important hazard(s): *Xi - Irritant* R 36/38 - Irritating to skin and eyes. R 43 - May cause sensitisation by skin contact. *S 24/25 - Avoid contact with skin and eyes.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317* https://www.ewg.org/guides/substances/5309-SANTALUMALBUMSANDALWOODOIL#.W3wkbehKiUk Some concern for skin allergies & irritation					
Tartaric Acid *(laevo-(+)-tartaric acid)*	Y		http://www.thegoodscentscompany.com/data/rw1034811.html European information : Most important hazard(s): *Xi - Irritant* *R 36/37/38 - Irritating to eyes, respiratory system, and skin.* *S 24/25 - Avoid contact with skin and eyes.* https://cosmeticsinfo.org/ingredient/tartaric-acid Safety Information: The Food and Drug Administration (FDA) has reviewed the safety of Potassium Sodium Tartrate and has affirmed its status as Generally Recognized as Safe (GRAS) as a direct food substance. FDA has approved the use of Tartaric Acid and Potassium Sodium Tartrate in Over-the-Counter (OTC) antacid drug products.					

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			More safety Information: Tartaric acid is metabolically inert in the human body. Link to FDA Code of Federal Regulations for Tartaric Acid https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1099&SearchTerm=tartaric%20acid https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=331.11&SearchTerm=tartaric%20acid Link to FDA Code of Federal Regulations for Potassium Sodium Tartrate https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=184.1804&SearchTerm=sodium%20potassium%20tartrate https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=331.11&SearchTerm=sodium%20potassium%20tartrate Tartaric Acid and its salts may be used in cosmetics and personal care products marketed in the Europe according to the https://cosmeticsinfo.org/glossary/letter_g#General_Provisions_of_the_Cosmetics_Regulation_of_the_European_Union Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013
TBHQ (*t-Butylhydroquinone*)		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr118.pdf https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR609.pdf https://pubchem.ncbi.nlm.nih.gov/compound/16043#section=GHS-Classification Signal: Warning GHS Hazard Statements *H312 (27.89%): Harmful in contact with skin [Warning Acute toxicity, dermal]* *H315 (20.64%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (32.21%): May cause an allergic skin reaction [Warning Sensitization, Skin]* Health Hazard SYMPTOMS: *Symptoms of exposure to this compound include irritation of the skin and eyes and dermatitis*. (NTP, 1992) https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+838 Clinical Effects: 0.2.1 SUMMARY OF EXPOSURE 0.2.1.1 ACUTE EXPOSURE ... D) WITH THERAPEUTIC USE 1) DERMAL: Localized contact dermatitis, pruritus, dry skin, burning, desquamation, erythema, brown or orange-brown nail discoloration, paradoxical ochronosis-like hyperpigmentation of the skin, and hypersensitivity reactions.
Terpineol	Y	Y	https://pubchem.ncbi.nlm.nih.gov/compound/17100#section=GHS-Classification Signal: Warning GHS Hazard Statements H315 (100%): Causes skin irritation [Warning Skin corrosion/irritation]

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			HUMAN EXPOSURE AND TOXICITY: In human subjects, alpha-terpineol had a low irritative potency but a strong odor. *Two dermatitis patients were reported to be sensitized to alpha-terpineol, although attempts to induce skin sensitization in volunteers using a dilute solution of alpha-terpineol were unsuccessful.* ANIMAL STUDIES*: In rabbits neat alpha-terpineol was a moderate skin irritant.* http://www.thegoodscentscompany.com/data/rw1011252.html#tosafty European information : Most important hazard(s): *Xi - Irritant* *R 36/38 - Irritating to skin and eyes.* S 24/25 - Avoid contact with skin and eyes. Hazards identification *Skin irritation (Category 2), H315*
Trichloromethyl Phenyl Carbinyl Acetate (*Rosacetol*)		Y	http://www.thegoodscentscompany.com/data/rw1002671.html#tosafty European information : Most important hazard(s): Xi - Irritant R 36/38 - Irritating to skin and eyes. S 24/25 - Avoid contact with skin and eyes.
Undecylenal *Undec-10-enal* *10-undecenal (aldehyde C-11 undecylenic)*	Y		https://www.ewg.org/guides/substances/15138-UNDECYLENAL#.W3sGQehKiUk This substance is Generally Recognized as Safe (GRAS) as a food additive by the US Food and Drug Administration *Only in: Household Cleaners* low Concer FDA - Priority based Assessment of Food Additive (PAFA) - U.S. Food and Drug Administration (FDA) http://www.thegoodscentscompany.com/data/rw1000332.html#tosafty Most important hazard(s): N - Dangerous for the environment. *R 36/38 - Irritating to skin and eyes.* *R 43 - May cause sensitisation by skin contact.* GHS Classification in accordance with 29 CFR 1910 (OSHA HCS) Acute toxicity, dermal (Category 5), H313 *Skin irritation (Category 2), H315* *Skin sensitisation (Category 1), H317* Signal word Warning Hazard statement(s) H313 - May be harmful in contact with skin H315 - Causes skin irritation H317 - May cause an allergic skin reaction https://pubchem.ncbi.nlm.nih.gov/compound/8187#section=GHS-Classification Signal: Warning GHS Hazard Statements *H315 (99.9%): Causes skin irritation [Warning Skin corrosion/irritation]* *H317 (91%): May cause an allergic skin reaction [Warning Sensitization, Skin]*

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
			EPA Safer Chemical 10-Undecenal - Yellow triangle - The chemical has met Safer Choice Criteria for its functional ingredient-class, but has some hazard profile issues. Specifically, a chemical with this code is not associated with a low level of hazard concern for all human health and environmental endpoints. (See Safer Choice Criteria). While it is a best-in-class chemical and among the safest available for a particular function, the function fulfilled by the chemical should be considered an area for safer chemistry innovation.
Vanillin	Y		http://www.thegoodscentscompany.com/data/rw1011712.html#tosafty https://chem.nlm.nih.gov/chemidplus/name/vanillin
Vetiveria Zizanoides Root Oil	Y		https://www.ewg.org/skindeep/ingredient/724810/VETIVERIA_ZIZANOIDES_ROOT_OIL/#.W3sAhuhKiUk Multiple, additive exposure sources *Irritation (skin, eyes, or lungs)* One or more animal studies show skin irritation at low doses RTECS®- Food and Cosmetics Toxicology Organ system toxicity (non-reproductive) Classified as not expected to be potentially toxic or harmful Environment Canada Domestic Substance List http://www.thegoodscentscompany.com/data/es1695591.html#tosafty Most important hazard(s): Xi - Irritant R 38 - Irritating to skin.

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
1-Phenylethyl acetate (*Methylphenylcarbinyl acetate*)	Y		http://www.thegoodscentscompany.com/data/rw1011092.html **European information :** **Most important hazard(s):** S 24/25 - Avoid contact with skin and eyes. **Signal word Warning**
3,7-Dimethylnona-2,6-dienentrile (*3,7-Dimethylnona-2,6-dienenitrile* *Homogeranyl nitrile* *Lemonile* (Givaudan))		Y	http://www.thegoodscentscompany.com/data/rw1042831.html#tosafty **European information :** **Most important hazard(s):** S 24/25 - Avoid contact with skin and eyes.
3, 7-Dimethylocta-2,6-dien-1-yl phenylacetate (*geranyl phenyl acetate*)	Y		**Trans-3,7-Dimethyl-2,6-octadien-1-yl phenylacetate or Geranyl phenylacetate ???**
4-(2,5,6,6-Tetramethylcyclohex-2-en-1-yl)but-3-en-2-one *(4-(2,5,6,6-Tetramethyl-2-cyclo-hexen-1-yl)-3-buten-2-one* *Methyl-alpha-ionone*)	Y		http://www.thegoodscentscompany.com/data/rw1006691.html#tosafty **European information :** **Most important hazard(s):** None - None found. S 24 - Avoid contact with skin.
Acetic acid, anhydride, reaction products with 1,5,10-trimethyl-1,5,9-cyclododecatriene		Y	https://pubchem.ncbi.nlm.nih.gov/compound/53422908#section=Safety-and-Hazards **Signal: Warning** **GHS Hazard Statements** H317 (97.13%): May cause an allergic skin reaction [Warning Sensitization, Skin] https://echa.europa.eu/substance-information/-/substanceinfo/100.105.384 Warning! According to the classification provided by companies to ECHA in REACH registrations this substance is very toxic to aquatic life, is very toxic to aquatic life with long lasting effects and may cause an allergic skin reaction.
Aloe Barbadensis Leaf Extract		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr274.pdf http://www.ema.europa.eu/docs/en_GB/document_library/Herbal_-_HMPC_assessment_report/2017/04/WC500225527.pdf
Amyris Balsamifera Bark Oil		Y	No Data

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
(*West Indian sandalwood oil*)			
Anthemis Nobilis Flower		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR653.pdf (Anthemis Nobilis Flower Extract, oil, water) Int J Toxicol. 2017 May/Jun;36(1_suppl):57S-66S. doi: 10.1177/1091581817705620. Safety Assessment of Anthemis nobilis-Derived Ingredients as Used in Cosmetics. Johnson W Jr, Heldreth B, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG Jr, Shank RC, Slaga TJ, Snyder PW, Andersen FA. Abstract Anthemis nobilis (Roman chamomile) flower extract, anthemis nobilis flower oil, anthemis nobilis flower powder, and anthemis nobilis flower water are ingredients that function as fragrance ingredients and skin-conditioning agents in cosmetic products. These ingredients are being used at concentrations up to 10% (anthemis nobilis flower water) in cosmetic products. The available data indicate that these 4 ingredients are not irritating or sensitizing. Chemical composition data and the low use concentrations suggest that systemic toxicity would not be likely if percutaneous absorption of constituents were to occur. Formulations may contain more than 1 botanical ingredient; each may contribute to the final concentration of a single component. Manufacturers were cautioned to avoid reaching levels of plant constituents that may cause sensitization or other adverse effects. Industry should continue to use good manufacturing practices to limit impurities in the ingredient before blending into cosmetic formulations. The Expert Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics, when formulated to be nonsensitizing.
Benzene, 1,2-dimethoxy- (*Veratrole* *1,2-dimethoxybenzene* *ortho-dimethyl hydroquinone*)	Y		No Data
Benzeneacetic acid, phenylmethyl ester (*Benzyl Phenylacetate*)	Y		No Data
Bulnesia sarmienti, ext. (*Bulnesia sarmientoi , verawood, Guaiol*)	Y		No Data
Caprylyl Alcohol	Y		Capryl alcohol or Caprylic alcohol????
Castoreum	Y		No Data
Celery seed (Apium graveolens L.)	Y		No Data
Chamomilla Recutita (Matricaria) Flower Oil	Y		https://www.cir-safety.org/sites/default/files/chamom032016tent.pdf
Citrus Aurantium Bergamia (Bergamot) Fruit Oil	Y		
Citrus Aurantium Dulcis (Orange) Peel Oil	Y		

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
Citrus Medica Limonum (Lemon) Peel Oil	Y		
Citrus Nobilis (Mandarin Orange) Peel Oil	Y		
Copper Chlorophyll	Y		https://cosmeticsinfo.org/ingredient/chlorophyllin-copper-complex-0 The Food and Drug Administration (FDA) has approved Chlorophyllin-Copper Complex as a color additive exempt from certification. As a color, Chlorophyllin-Copper Complex may be safely used for coloring dentifrices when it conforms to FDA specifications. FDA has also permits the use of Chlorophyllin-Copper Complex in Over-the-Counter (OTC) internal deodorant drug products. Internal deodorant drug products are taken internally to reduce odors from conditions such as colostomies, ileostomies or fecal incontinence. More safety Information: All color additives used in foods, drugs and cosmetics in the United States must be approved by FDA and listed in the Code of Federal Regulations. In some cases, FDA requires that each batch of color produced for use in regulated products can be used only if it is certified by the agency to meet strict specifications. FDA maintains a laboratory especially for this purpose and color manufacturers must pay a fee to support this activity. FDA only approves colors after extensive review of all safety data and publication of the basis for its approval in the Federal Register. Link to FDA Code of Federal Regulations for Chlorophyllin Copper Complex https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=357.810&SearchTerm=chlorophyllin-copper https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=73.2125&SearchTerm=chlorophyllin-copper Chlorophyllin-Copper Complex is listed as CI 75810 in the Cosmetics Directive of the European Union and may be used as a coloring agent in all cosmetics and personal care products (see Annex IV). When used in cosmetic products in the European Union, this ingredient must be called CI 75810. Link to the EU Cosmetic Regulation: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=LEGISSUM:co0013 You can learn more about the regulation and labeling of colors at: https://www.personalcarecouncil.org/colors-cosmetics-regulation-and-nomenclature-united-states
Evernia Prunastri (Oakmoss) Extract (*evernia prunastri lichen extract*)	Y		No Data
Hex-3-en-1-yl acetate (*3-Hexenyl acetate, (3E)-)*	Y		http://www.thegoodscentscompany.com/data/rw1130931.html#tosafty **European information :** **Most important hazard(s):** S 24/25 - Avoid contact with skin and eyes.
Methyl 2-(methylamino)benzoate (*Methyl N,N-dimethylanthranilate*)	Y		No data
Methyl Hydrogenated Rosinate	Y	Y	No data

Ingredient List – Johnson's Baby Powder & Shower-to-Shower			
Chemical	**Baby Powder**	**Shower-to-Shower**	
Musk Ketone		Y	https://echa.europa.eu/documents/10162/e6a84904-118b-447a-8766-f7bda48f7ce0 https://pubchem.ncbi.nlm.nih.gov/compound/6669#section=Safety-and-Hazards **Signal: Warning** **GHS Hazard Statements** ***H351 (99.74%): Suspected of causing cancer [Warning Carcinogenicity]***
Nonyl Acetate	Y		https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/pr469.pdf https://pubchem.ncbi.nlm.nih.gov/compound/8918#section=Safety-and-Hazards http://www.thegoodscentscompany.com/data/rw1015611.html#tosafty **European information :** **Most important hazard(s):** ***S 24/25 - Avoid contact with skin and eyes***.
Oils, styrax	Y		No data
Orris concrete (Iris pallida) (*orris rhizome concrete butter (iris pallida)*)	Y		http://www.thegoodscentscompany.com/search3.php?qName=orris+rhizome+concrete+butter+%28iris+pallida%29&submit.x=0&submit.y=0 **European information :** **Most important hazard(s):** ***S 24/25 - Avoid contact with skin and eyes.***
Indisan (Sandela) reaction product (*Sandela*)		Y	Sandela
Tanacetum vulgare, ext.	Y		No data
Thymus Vulgaris (Thyme) Oil	Y		
Tromethamine		Y	https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/PR630.pdf
Undecan-2-one	Y		http://www.thegoodscentscompany.com/data/rw1021151.html#tosafty **European information :** **Most important hazard(s):** S 24/25 - Avoid contact with skin and eyes.
1,5-Dimethyl-1-vinylhex-4-en-1-yl benzoate	Y		https://pubchem.ncbi.nlm.nih.gov/compound/Linalyl_benzoate#section=Cellular-Locations http://www.thegoodscentscompany.com/data/rw1030541.html

APPENDIX E

Photographs of Body Powder Products and Their Warnings


CLINICALLY
mildness
PROVEN®
Johnson's®
baby
powder
talco para bebes
keeps skin comfortable,
dry & feeling soft all day
no parabens, phthalates or dyes
Johnson & Johnson
22 OZ (623g)
30039151


For over 125 years JOHNSON'S® formulas have been specially designed for baby's unique and delicate skin. Great for kids and adults too!
Hypoallergenic & tested with dermatologists
TO USE:
1. Shake powder directly into your hand, away from the face, before smoothing onto the skin.
2. Close tightly after use, store in a cool, dry place.
PARA USAR:
1. Antes de aplicarlo sobre la piel, agitar el polvo directamente en la mano, lejos de la cara.
2. Cerrar bien después de usar, y guardar en un lugar fresco y seco.
Every JOHNSON'S® product is designed to meet or exceed the top internationally recognized regulatory standards. Learn more at www.johnsonsbaby.com
INGREDIENTS: Talc*, Fragrance
*naturally-derived ingredients
WARNING: Keep powder away from child's face to avoid inhalation, which can cause breathing problems. Avoid contact with eyes. For external use only. Close tightly after use. Keep out of reach of children. Do not use if quality seal is broken.
ADVERTENCIA: Mantener el talco alejado de la cara del niño para evitar la inhalación, que podría causar problemas respiratorios. Evitar el contacto con los ojos. Para uso externo exclusivamente. Cerrar bien después de usar. Mantener fuera del alcance de los niños. No usar si el sello de seguridad está roto.
Questions? 866-JNJ-BABY;
Outside US, dial collect 215-273-8755.
¿Preguntas? 866-JNJ-BABY;
Fuera de los EE. UU., llamada de cobro revertido al 215-273-8755.
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JOHNSON & JOHNSON CONSUMER INC.
Skillman, NJ 08558
© J&JCI 2018
Talc Made in China
Talco hecho en China
Care To Recycle™ our babies will inherit our planet®
30039152
3 81370 03014 0


Angel Of mine™
Baby Powder
• Fresh, Clean & Soft
NET WT. 14 OZ (397 g)


LOT#18008W
Angel Of mine™
ANGEL OF MINE™ Baby Powder is especially formulated to soothe and give a fresh, clean and fragrant feeling to your baby's delicate skin. Made of the finest talc, it helps to absorb excess moisture, keeping the baby's skin dry and soft for ultimate comfort.
Directions: After changing diapers and after every bath, dry baby's skin thoroughly and apply liberally as needed.
Ingredients: Talc and Fragrance.
Warnings: • Keep out of reach of children. • For external use only. • Avoid contact with eyes, discontinue use if irritation persists. • Avoid ingestion or accidental inhalation by baby. This product contains talcum powder and is intended for external use only. Frequent application of talcum powder in the female genital area may increase the risk of ovarian cancer. Seek professional assistance if needed.
This product is sold by weight, not volume. Settling will occur during handling & shipping.
7 81072 01021 9
983408 DISTRIBUTED BY
GREENBRIER INTERNATIONAL, INC.
500 VOLVO PARKWAY, CHESAPEAKE, VA 23320
MADE IN U.S.A.


ASSURED
Shower
& Bath
Absorbent
Body Powder
with
Lavender
Compare to
Shower to Shower®
NET WT 13oz (368 g)
18101 072
ASSURED
Assured's Shower & Bath Absorbent Body Powder is specially made with cornstarch for greater absorbancy and baking soda to help neutralize odor. This Shower & Bath product is uniquely formulated to help you feel cool and confident all day.
CAUTION: Discontinue use if rash or irritation develops. Do not apply to broken or irritated skin.
WARNING: This product contains talcum powder and is intended for external use only. Frequent application of talcum powder in the female genital area may increase the risk of ovarian cancer.
KEEP OUT OF REACH OF CHILDREN
INGREDIENTS: Talc, Cornstarch, Sodium Bicarbonate, Fragrance, Tricalcium Phosphate, Polysaccharides, Aloe Barbadensis Extract, Chamomile (Anthemis Nobilis) Extract.
*This product is not manufactured or distributed by Johnson & Johnson, owner of the registered trademark Shower to Shower®
DISTRIBUTED BY
GREENBRIER INTERNATIONAL, INC
CHESAPEAKE, VA. 23320
PRODUCT OF USA
6 39277 17468 0


Spring Fresh®
Poudre Powder Talco
Tranquil Breeze
Brise fraîche Brisa fresca
NET WT. 5.0 OZ
140 g


INGREDIENTS: TALC, FRAGRANCE (PARFUM), BENZYL BENZOATE, BENZYL CINNAMATE, BENZYL SALICYLATE, CITRONELLOL, EUGENOL, ALPHA-ISOMETHYL IONONE, HEXYL CINNAMAL, HYDROXYISOHEXYL 3-CYCLOHEXENE CARBOXALDEHYDE, HYDROXYCITRONELLAL, BUTYLPHENYL METHYLPROPIONAL, LIMONENE, LINALOOL.
INGREDIENTES: TALCO, FRAGANCIA, BENZOATO DE BENCILO, CINAMATO DE BENCILO, SALICILATO DE BENCILO, CITRONELOL, EUGENOL, ALFA-ISOMETIL IONONE, HEXIL CINNAMAL, HIDROXI-ISOHEXIL 3-CICLOHEXENO CARBALDEHÍDO, HIDROXICITRONELAL, BUTILFENIL METILPROPIONAL, LIMONENO, LINALOOL.
Caution: For adult use only. Keep out of reach of children. If the product enters the eye, wash out thoroughly with plenty of clean water. Keep powder away from children's nose and mouth.
Medical evidence suggests that women who use talcum powder as a feminine hygiene product run a greater risk of developing ovarian cancer.
Mise en garde: Pour adultes seulement. Garder hors de la portée des enfants. Si le produit entre en contact avec les yeux, rincer abondamment à grande eau. Garder la poudre loin du nez et de la bouche des enfants. Les preuves médicales suggèrent fortement que les femmes utilisant la poudre de talc comme produit d'hygiène féminine courent un plus grand risque de développer un cancer de l'ovaire.
Precaución: Solo para uso en adultos. Mantén este producto fuera del alcance de los niños. Si el producto entra en contacto con los ojos, enjuágatelos con abundante agua limpia. Mantén el polvo alejado de la nariz y la boca de los ninõs. La evidencia médica sugiere que las mujeres que usan talco como producto de higiene femenina tienen un riesgo mayor de desarrollar cáncer ovárico.
Belcam Inc., Rouses Point, NY 12979-0277 USA
Imported for / Importé pour / Importado por: Belcam Inc., Candiac, QC J5R 3L5 Canada
Proudly made in U.S.A. Fabriqué avec fierté aux États-Unis Hecho con orugllo en EUA
0 38949 00674 6
12M
www.belcamshop.com
tranquil breeze LB-0067R2


equate™
Compare to Dr. Scholl's® Soothing Foot Powder*
Soothing Foot Powder
• Helps cool feet
• Absorbs excess moisture
• Helps control foot odor
Made in the USA
Factory Certified
NET WT 7 OZ (198 g)


Equate™ Soothing Foot Powder refreshes your feet.
• Highly absorbent formula helps keep feet dry and comfortable
• Cooling ingredient soothes and refreshes
• Regular use helps control foot odor
Ingredients
Talc, salicylic acid, methyl salicylate
Directions
• Sprinkle generously on all areas of the feet.
• Not intended for genital area.
Warnings
For external use only.
Keep out of reach of children.
If swallowed, get medical help or contact a Poison Control Center right away.
Other information
• Bottle contains the proper weight.
• Contents may settle during shipping.
Questions?
Call 1-888-287-1915

Exhibit 51

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF ARCH CARSON, MD, PHD

Date: November 16, 2018

Arch Carson, MD, PhD

Talcum Powder and Ovarian Cancer

1. Introduction

I was asked to explain the relationship between the regular perineal use of talc-based personal hygiene products and the subsequent development of ovarian cancer in their users. I intend this report to explain this relationship. I will describe ovarian cancer, what is known about its natural history, and will present statistics regarding its incidence, prevalence and fatality. I will then describe what talc is and why talcum powder is used in personal care products. I will then present the scientific evidence linking talc-based personal hygiene products and their components with cancer, and will show how the various components of this evidence, along with other data, lead me to conclude that regular perineal application of talcum powder products causes ovarian cancer in some users, and raises the risk of ovarian cancer in all users.

2. Qualifications

I am a physician who specializes in the practice of medical toxicology. I am currently an Associate Professor at the University of Texas School of Public Health in Houston and the Program Director of the Occupational and Environmental Medicine Residency training program at the University of Texas Health Science Center at Houston. I received my medical degree from the Ohio State University and a doctor of philosophy degree in Toxicology from the Kettering Laboratory at the University of Cincinnati. I am board certified by the American Board of Preventive Medicine in Occupational Medicine, and have been in the continuous practice of medical toxicology since 1991. My professional activities have included patient care, basic and applied research, teaching of medical students, graduate students and post-graduate medical trainees, and professional consulting. I have been a program director of the NIOSH-funded Education and Research Center at the University of Texas for 19 of the last 21 years. Other major collaborations include as Liaison for the World Health Organization Collaborating Centre in Occupational Health and as environmental exposure consultant to the MD Anderson Cancer Center in Houston. My curriculum vitae is attached to this report as Exhibit A.

3. Information reviewed and methodology employed

In the preparation of this report, I have reviewed relevant published scientific and medical literature, reports and documents produced in the process of litigation, and various other documents and websites that I believed to be pertinent to the refinement or extension of my professional opinions. I applied the same methodology and scientific rigor in this research that I use in my academic and clinical practice. Documents and other sources which I considered in reaching my opinions are listed in Exhibit B, "Materials and Data Considered."

4. What is ovarian cancer?
   a. What is cancer?

   All types of cancer involve the uncontrolled growth and accumulation or dissemination of cells that originated from normal cells, but have been altered so that they behave differently. The many cells of a single cancer that result from this change are typically all derived from a single progenitor cell, and represent a clone of cells. When this clone

reaches sufficient numbers, the cells themselves may develop into a recognizable "mass" that is called a tumor. Tumors may cause symptoms and other health problems simply by taking up space and putting pressure on neighboring structures or blocking important fluid channels or nerves, thus disrupting normal functions of the body. Still other cancers can proliferate into the blood stream. As the number of cancerous cells increase, the biochemically active substances that they produce can also become a problem resulting in abnormal biological responses throughout the body. Some substances that might become a problem in this way include normal or abnormal hormones, enzymes, antibodies, and proteins. Cancerous cells are considered malignant if they lose their normal tendency to stop proliferating when they have filled a space or the bounds of their particular tissue type, referred to as contact inhibition. Malignant cells ignore these boundary cues and may invade other tissue spaces and organs with devastating results. They may also migrate via the blood stream or other routes to distant sites within the body where they set up a new location of tumor growth and tissue invasion. This process is called metastasis. Typically, cancers are not diagnosed until they produce sufficient symptoms or biochemical abnormalities that lead to an exhaustive diagnostic search resulting in their discovery. Occasionally, cancers are discovered accidentally as part of another investigation, e.g. a chest x-ray may find an asymptomatic lung cancer; a blood test may disclose a telltale abnormality. Still fewer cancers are discovered before they cause health problems through screening tests that are sensitive and specific enough to detect common cancers at a preclinical and hopefully highly treatable stage, e.g. routine colonoscopies to detect colon cancer, or PSA blood tests to detect prostate cancer.

b. Carcinogenesis-a two-step process

The process of normal cells becoming cancer cells is generally recognized as resulting from a two-step process.

Initiation. During initiation, a change is produced at one or more places in the DNA of a cell's chromosomes. Because the DNA represents the genetic code that becomes duplicated and passed along to cells that arise from it, when that cell divides to produce two cells, the change to the genetic code is also duplicated and is present in both of them.

Normally, the abnormal cell that results from a change in the genetic code cannot survive because its cellular machinery is also abnormal and poorly or non-functional. Less often, if the cell is able to survive in the body, it is still abnormal and deformed, and is recognized by the body's immune system as alien. The immune system attacks it and destroys it, and it does not survive. In the very rare instance that an alteration to the genetic material results in a survivable hereditary change that is not fatal, and which can escape the surveillance of the body's immune system, the resulting clone may live and persist. (Coussens LM, 2002)

Promotion - Once a cancer clone has been produced, it is at risk for being discovered and destroyed by the body's immune system, or failing to thrive in an environment for which it is not suited. Promotion is the process by which the cancer clone is shielded

from the body's defenses and is stimulated to undergo rapid growth, transforming a microscopic cancer clone into a self-sustaining symptomatic cancer over time. (Ferrante D, 2007) (Coussens LM, 2002)

Most known carcinogenesis events occur by the two-step process and involve a long latent period between the moment of the alteration in the genetic material and the recognition that a cancer is present. In human cancers, this latent period is often several months to many years in length. The latency period for ovarian cancer, generally, and for cancers induced by environmental agents is usually quite long, often >20 years. (Nadler DL, 2014) Promotion occurs throughout the latent period and stimulates the growing cancerous cells to become a recognizable cancer. A third stage in the natural history of a cancer, referred to as Progression, involves maturation, differentiation or de-differentiation and accumulation of transcriptional changes that solidify the tumor's growth rate and invasiveness. Some carcinogenic substances are initiators and some are promotors, and still others are called complete carcinogens because they are capable of initiation and promotion.

c. Ovarian cancer

Ovarian cancer is a group of cancers that arise in the ovary or in adjacent tissues. It is estimated that about 22,240 women will receive a new diagnosis of ovarian cancer and about 14,070 women will die from ovarian cancer in the United States in 2018. (American Cancer Society, n.d.) (Torre LA, 2018) Ovarian cancer ranks fifth in cancer deaths among women, and first due to cancers of the female reproductive system. Most ovarian cancers are not discovered until they have reached an advanced stage and have spread to sites elsewhere in the body. Because advanced ovarian cancers are more difficult to treat, they have a high fatality rate. For these reasons, any effective prevention of ovarian cancer or reduction in ovarian cancer risk can have a significant impact on this disease and can save many women's lives.

There are several recognized forms of ovarian cancer that are distinguished by the specific tissues from which they arise, or the microscopic characteristics of the tumor cells themselves. About 85% to 90% of malignant ovarian cancers are epithelial ovarian carcinomas, and the majority of these are of the serous type (American Cancer Society, n.d.) (Prat, 2015). Ovarian, fallopian tube, and peritoneal cancers have a similar clinical presentation and are treated similarly, and current evidence suggests that they may have a common origin, supporting a common staging system (Soong TR, 2018).

Despite significant advances in cancer diagnosis and therapies over the past several decades, there have been few changes in the incidence or fatality rates for ovarian cancer. Consequently, it is worth considering preventable environmental causes of the ovarian cancer epidemic. (Woodruff, 1979) (LA Torre, 2018)

5. What is talc?
   a. General

Talc is a hydrated magnesium silicate mineral produced through a metamorphic geological process and having the generalized chemical formula $Mg_3Si_4O_{10}(OH)_2$. Some substitution of atoms occurs in variations of talc found in nature. Small amounts of Aluminum (Al) or Titanium (Ti) can substitute for Silicon, and small amounts of Iron (Fe), Manganese (Mn), Aluminum (Al) and Calcium (Ca) can substitute for Magnesium. This produces slight variations in the color, hardness and chemical properties of the mineral. Talc is the softest mineral on the Mohs Hardness Scale. (King, n.d.) It is essentially insoluble in water, but is slightly soluble in dilute mineral acids. The process seems to involve the extraction of magnesium and other cations leaving only the silicate as silicic acid and silica.

The commercial value of talc stems from its crystalline structure. Most talc is present in natural deposits as the platy form of talc, in which the talc crystals are arrange in large flat sheets running parallel to one another. These sheets are attracted to each other by weak Van der Waals forces that can be easily overcome by mechanical forces, causing the sheets to slide on each other. On the macro scale, this property gives talc its characteristic slippery feeling on the skin. The platy structure also gives talc its ability to absorb moisture and oil. Some talc is found as a fibrous crystalline structure, similar to some asbestos, also a magnesium silicate mineral. In fact, these two minerals are closely related in terms of their formation and composition. Talc deposits are often intermingled with asbestos and vice versa. (Rohl, 1974) (Rohl AN, 1976) (National Institute for Occupational Safety and Health, 2011) (Lockey, 1981)

b. Talcum Powder and Cancer.

Numerous studies have examined the cancer causing characteristics of talc. (Wild, 2006) Talc has caused cancer when implanted in various tissues and under the skin in laboratory animals. It causes inflammation and fibrotic reaction, including the chemotaxis of inflammatory immune cells, and accelerated growth and division of cells in the involved tissues (Okada, 2007). This is a normal body process that leads to the thwarting of infection and rapid healing, but in the absence of tissue injury, accelerated growth and cell division has the effect of amplifying and propagating viable genetic mutations, leading to cancer. Talc particles have been repeatedly demonstrated in ovarian tumor tissues (Henderson WJ C. J., 1971) (Henderson WJ T. H., 1979) and in inflammatory tissue in otherwise normal ovaries (Mostafa SAM, 1985). In 2006, the International Agency for Research on Cancer (IARC) evaluated the published evidence for the carcinogenicity of talc, not containing asbestiform fibers, when inhaled into the respiratory system and when applied to the perineum in personal hygiene activities. The agency concluded that talcum powder is a “possible human carcinogen” (Group 2B) when applied to the perineum, meaning that there is insufficient evidence of carcinogenesis in humans, but strong evidence in other mammalian species. IARC also concluded that there was insufficient evidence of carcinogenicity by the inhalation route (Group 3). (International Agency for Research on Cancer, 2010) Since that time,

numerous other studies have added to the data on this issue. A recent meta-analysis showed that talc workers do have an excess of lung cancers. (Chang C-J, 2017)

When implanted under the skin or into tissues of laboratory animals, talcum powder induces an inflammatory response. This reaction involves the chemotaxis of inflammatory cells of the immune system, lymphocytes, neutrophils and macrophages, the release of cytokines that promote membrane permeability and stimulate cell division. As this reaction matures over time, granulomas may begin to develop. All of this signifies that talcum powder is an effective and potent promotor of already initiated genetic alterations. (Fletcher NM M. I., 2018) (Fletcher NM S. G., 2018) (Saed GM, 2017) (Radić I, 1988) (Okada, 2007) Other studies have demonstrated the ability of these same reactions to satisfy the carcinogenic initiation step, characterizing talcum powder as a complete carcinogen. (Shukla A, 2009) (Fletcher NM M. I., 2018)

c. What about asbestos and other components in talc and talc-based products?

Talcum powder products in the marketplace have been shown to contain asbestos. (Paoletti L, 1984) (VanOrden D, 2000) (VanGosen BS, 2004) (Longo WE, 2017) Asbestos is conclusively recognized as a cause of ovarian cancers. The IARC Working Group concluded that "a causal association between exposure to asbestos and cancer of the ovary was clearly established, based on five strongly positive cohort mortality studies of women with heavy occupational exposure to asbestos, (International Agency for Research on Cancer, 2012)" and "studies showing that women and girls with environmental, but not occupational exposure to asbestos had positive, though non-significant, increases in both ovarian cancer incidence and mortality. (Acheson ED, 1982) (Fox, 1982) (Berry G, 2000) (Newhouse ML, 1972) (Reid A H. J., 2008) (Reid A S. A., 2009) (Pira E, 2005) (Magnani C, 2008) (Bertolotti M, 2008) (Ferrante D, 2007) (Germani D, 1999) (Rösler JA, 1994) The classification determined by IARC included all forms of asbestos and talc containing asbestiform fibers (fibrous talc). I have seen evidence that Johnson & Johnson's talcum powder products contain asbestos and fibrous talc.[1]

d. Carcinogenic metals in talcum powder

In addition to other related minerals, talcum powder may contain varying amounts of chromium, cobalt and nickel, metal ions that are recognized as cancer causing. These ions leach out of the talcum powder slowly over time, resulting in continuous, low-level exposure of the surrounding tissues to carcinogenic metals. (Jurinski JB, 2001) I have seen evidence that Johnson & Johnson's talcum powder products contain nickel (Group 1

[1] Ex. 28, Hopkins Dep. (Aug. 16 & 17, 2018; Oct. 26, 2018; and Nov. 5, 2018); Ex. 47, Pier Dep. (Sept. 12 & 13, 2018); Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD (Nov. 14, 2018)

human carcinogen), chromium (Group 1 human carcinogen), and cobalt (Group 2B-possible human carcinogen).[2]

e. Other potentially cancer-causing constituents

Johnson & Johnson's Baby Powder and Shower to Shower contain numerous ingredients that have been added to the products, i.e. fragrance chemicals, some of which have been shown to produce cancer in laboratory animals. These substances are likely to be present in very small or trace quantities, and likely present a lower level of risk than the major components, by mass. Nonetheless, any additional risks are added as part of a total risk profile. I have reviewed the report of Dr. Michael Crowley and agree with his conclusions that these chemicals may contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products.[3]

6. Epidemiology linking talcum powder and ovarian cancer

Many research studies have shown a strong association between talcum powder exposure and the development of ovarian cancer. (Langseth H, 2008) (Terry KL, 2013) (Schildkraut JM, 2016) (Trabert, 2016) (Berge W, 2017) (Cramer Daniel W, 2016) (Penninkilampi R, 2018)

a. What evidence links exposure to talcum powder products with ovarian cancer?

Multiple epidemiological studies have examined the link between the personal hygiene use of talc containing products and the occurrence of ovarian cancers (Booth M, 1989) (Cook LS K. M., 1997) (Cook LS e. a., 1997) (Cramer DW, 1982) (Whittemore AS, 1988) (Harlow BL W. B., 1989) (Chen Y, 1992) (Harlow BL C. D., 1992) (Rosenblatt KA, 1992) (Hartge P, 1988) (Tzonou A, 1993) (Chang S, 1997) (Heller DS, 1996) (Penninkilampi R, 2018). Talcum powder causes proliferation of human (Prat, 2015) ovarian cells in culture (Buz'Zard AR, 2007), and causes these cells to express reactive oxygen species (ROS) (Buz'Zard AR, 2007).

The research investigating the link between talcum powder exposure and ovarian cancer has been reviewed as a scientific whole at multiple stages. (Harlow BL H. P., 1995) (Ness Roberta B, 1999) (Muscat JE, 2008) (Terry KL, 2013) (Berge W, 2017) (Penninkilampi R, 2018)

Laboratory, animal and human studies support the conclusions that talc causes ovarian cancer, and have filled in the blanks that establish biological plausibility and scientific coherence. (Jaiswal M, 2000) (Balkwill Fran, 2001) (Okada, 2007) (Saed Ghassan M, 2017) (Harper, 2019)

7. Talcum powder product use

[2] Ex. 47, Pier Dep. (Sept. 12 & 13, 2018)

[3] Expert Report of Michael Crowley, PhD (Nov. 12, 2018).

Numerous studies have interviewed women regarding their personal practices of application of talc-based powders to the perineal area. Due to variations in these practices, it has been difficult to estimate dose in order to evaluate the dose response relationship for ovarian cancer. It is also difficult to exactly estimate the quantity of talcum powder administration during personal hygiene activities. For studies that attempted to determine amount of exposure, most relied on a method of estimating the frequency of application and/or the duration of those practices, then simply multiplying to reach a total number of applications over time. (Harlow BL H. P., 1995) (Langseth H, 2008) A review of studies of perineal talcum powder or cornstarch application suggests that the use of cornstarch instead of talcum powder reduces the risk of ovarian cancer. (Whysner J, 2000)

8. Other evidence
    a. Transport of talc-containing materials from the perineum to the upper reproductive tract and body cavities has been shown to occur with startling regularity and with respect to a wide variety of particulate materials. (Egli GE, 1961) (Venter PF, 1979) (Blumenkrantz MJ, 1981) (Halme J, 1984) (Sjösten ACE, 2004) Clearly, sufficient particulate materials applied routinely to the perineum have ready access and in sufficient quantities to produce biological responses in internal tissues, including the ovaries and surrounding structures. There are a limited number of animal studies suggesting that this transport does not occur. (National Toxicology Program, 1993) These are not as compelling as the human evidence because of anatomical and physiological differences between animals and humans in this regard, as well as the overwhelming evidence in humans.

9. Conclusions and opinions

The following conclusions and opinions are expressed with respect to reasonable medical and scientific certainty and I have applied reliable scientific principles and methods to the facts in reaching them. These opinions are based upon the documents and literature reviewed and cited herein, and also upon my own professional training and experience in practice of medicine and medical toxicology.

I. Talcum powder products sold for personal hygiene use are carcinogenic.

Talcum powder is immunogenic, producing chronic inflammation in the tissues in which it sequesters, with the attraction of lymphocytes and macrophages and the ongoing local release of pro-inflammatory cytokines and reactive oxygen species. Further, all talcum powder has some component of mineral fibers that are toxic to macrophages and intensify the inflammatory response and stimulate cell growth and proliferation. The presence of asbestos, fibrous talc, carcinogenic metals and other chemicals further intensify this effect. Cohort and case-control studies have shown statistically significant associations between talc-based powder use and ovarian cancers. The presence of carcinogenic metals such as, chromium, cobalt and nickel, and toxic fragrance components in commercial talcum powder products, adds to their carcinogenic potency. Talcum powder is a complete carcinogen and can both initiate and promote the development of cancers in the tissues in which it sequesters.

II. Perineal use of talcum powder products for feminine hygiene purposes results in direct exposure to the female reproductive tract.

A proportion of talcum powder from personal hygiene applications to the perineum is transported or migrates through the reproductive tract, through the patent fallopian tubes, onto the ovaries and into the pelvic cavity. Talc particles have been identified in reproductive system structures of women who utilize talc powders. These include the uterine cervix, the endometrium, the fallopian tubes and the ovaries. Inhalation is likely a secondary route of exposure.

III. Common carcinogenic constituents of talcum powder products participate in and add to the carcinogenic process.

Naturally occurring carcinogenic components of talcum powder, i.e. asbestos, chromium, nickel, and cobalt, are liberated in bodily fluids and tissues and are free to exert their carcinogenic effects. Added substances that are toxic or carcinogenic, i.e. fragrance chemicals, may also contribute to these effects. This process is the most intense where the duration is the longest. Because the ovaries have no intrinsic elimination system, the transport of talc particles and their constituents reaches the ovaries where it stalls and sequesters. For these reasons, ovarian tissue is most at risk for the carcinogenic effect of these substances.

IV. Regular perineal application of talcum powder products causes epithelial ovarian cancer in some users, and raises the risk of ovarian cancer in all users.

Multiple case-control and cohort epidemiological studies have looked at the relationship between the perineal use of talc-based powders and the eventual development of epithelial ovarian cancer. Most, but not all, of these studies show a consistent positive relationship. When confounding and bias are exhaustively considered, the positive association remains. I conclude that the apparent cause and effect relationship between perineal talcum powder use and ovarian cancer is real, amounting to about a 30% increased risk of ovarian cancer in talcum powder product users. At the current rate of ovarian cancer diagnosis and mortality, elimination of this source of risk could result in over 3,000 lives saved in the U.S. each year.

In 1965, Sir Austin Bradford Hill published what has come to be recognized as the best collection of factors to consider for the assessment of scientific evidence that relates the causation of disease to environmental exposures (Hill, 1965). These factors include: (1) Strength of association, (2) Consistency of the evidence, (3) Specificity, (4) Temporality, (5) Biological gradient, (6) Plausibility, (7) Coherence, (8) Experiment, and (9) Analogy. Below I provide my evaluation of the scientific evidence with respect to the Hill factors.

Strength of association –Many epidemiological studies have attempted to examine the association between perineal use of talcum powder products and ovarian cancer. Most of these have been case-control studies, where women diagnosed with ovarian cancer are paired with others of similar demographic background who do not have ovarian cancer. All of these women are interviewed about their past practices and exposures, including the use of talcum powder products. The resulting data are analyzed to compute an odds ratio (OR) that describes the

likelihood of those with cancer having had greater exposure to talcum powder than those who did not. Cohort studies selected populations of women, assessing them for many factors, including perineal talcum powder use, and followed them over time counting the occurrences of ovarian cancers. These studies were than able to compute a relative risk (RR) of exposure to talcum powder resulting in ovarian cancers. Of more than 25 case-control studies in the literature, the heavy majority showed positive and significant ORs for perineal talcum powder use and ovarian cancer. The three cohort studies did not find a significant relative risk of perineal talcum powder exposure leading to ovarian cancer, but did show positive non-significant trends. Several research groups have looked at the totality of the research evidence, evaluated the published study reports, and have reanalyzed those data on a common playing field through meta-analyses. Taken in their totality, and accounting for sources of bias and differing statistical treatments, these epidemiological studies support a strong association between the perineal use of talcum powder and ovarian cancer.

Consistency of the evidence – As stated above, the majority of epidemiological studies that have investigated the link between perineal talcum powder use and ovarian cancer have reported positive associations. These studies are consistent in their findings of a relationship between perineal use of talcum powder products and the development of ovarian cancer. Further, recent meta-analyses of previously published studies have verified the comparability of the research methods used and the consensus of conclusions.

Specificity – Specificity is the concept that a specific disease, rather than a host of diseases, is produced by a particular exposure, and that the exposure is a principal cause of the disease. Although talcum powder is known to cause non-specific inflammation in many tissues where its residues locate, the stimulation of ovarian cancer is particularly associated with the presence of talc in the ovaries and fallopian tubes. Of known factors associated with ovarian cancer, i.e. nulliparous state, early menarche, late menopause, oral contraceptive use, living in the twentieth century and beyond, perineal talcum powder exposure is proving to be prominent among them.

Temporality – If a particular exposure is the cause of a particular disease, then the onset of exposure should precede the onset of the disease. Studies investigating the link between perineal talcum powder exposure and ovarian cancer are designed to compare those with prior exposure to those who are not exposed, and so the scientific evidence supports this consideration.

Biological gradient – A basic toxicological principle is that a greater exposure intensity will result in a larger proportion of those exposed expressing the toxic effect, in this case ovarian cancer. In order to determine the intensity of a long-term environmental exposure, typically a measure of frequency or quantity of use is multiplied by the duration of such use. This allows categorization of exposure levels and comparisons. Although some studies have failed to find evidence of a dose-response relationship, several more recent reports have shown a clear dose-response when the number of subjects rose to a level producing sufficient statistical power to allow the analysis after subdivision of subjects into pertinent categorical groups, and frequency and duration were measured (Schildkraut JM, 2016) (Cramer Daniel W, 2016) (Wu, et al., 2009).

Plausibility – This factor expects the rational presentation of a mechanism whereby the exposure in question leads to the disease. Thus, if no such mechanism can be proposed, it is less likely that causation will be supported. In the case of ovarian cancer, the mechanism supported in the literature is as follows: Talcum powder products are applied to the perineal area in the course of routine personal hygiene practices. This element is supported by the existence of these products in the marketplace for many years and the statements of subjects interviewed for the purpose of conducting the scientific research discussed elsewhere in this report. Portions of the applied powders are transferred via active processes or passive mass action movements into the female reproductive tract, some making it all the way to the distal fallopian tubes, the ovary surfaces and the pelvic and peritoneal cavities. This element is supported by the observations that particulate materials of differing variety can make their ways along these pathways to the listed destinations, and the finding and confirmation of talc particles in normal ovarian tissues and ovarian tumor tissues at the time of oophorectomy or autopsy. Once reaching the target tissues, talcum powder and its constituents initiate carcinogenesis via multiple means, including, inflammation with chemotaxis of inflammatory cells, liberation of cytokines, and reactive oxygen species, inactivation of TP53 genetic modulator, inhibition of DNA repair, and long-term promotion of genetic mutations via continuous inflammation and cellular growth stimulation.

Coherence – The proposed cause and effect relationship should not "seriously conflict with the generally known facts of the natural history and biology of the disease."(Hill, 1965) The proposal that talcum powder product use results in the occurrence of ovarian cancer is entirely consistent with what is known about other factors related to ovarian cancer, i.e. early menarche, late menopause, pregnancies, breastfeeding history, oral contraceptive use, etc. All are factors that influence the local inflammatory environment of the ovary and its surroundings and have the potential to promote existing transcriptional errors and mutations.

Experiment – Interventions, such as tubal ligation that decreases the incidence of ovarian cancer by blocking the exposure route, offers experimental support for this mechanism. The use of cornstarch-based dusting powders as a substitute for talcum powder products offers additional experimental support.

Analogy – Have there been other environmental exposures that have been associated with ovarian cancers that act via similar mechanisms? Talcum powder is somewhat unique in terms of its delivery mechanism. But beyond that, the case of asbestos exposure is similar. Asbestos exposure has resulted in excesses of ovarian cancers in exposed women, although the route of exposure is thought to be by inhalation. Nonetheless, asbestos is a mineral very similar both chemically and structurally to talc that has been found in the ovary and peritoneal cavity of exposed women. The mechanisms of carcinogenesis for both asbestos and talc are similar and analogous. Further, talc-based products contain asbestos and non-asbestos mineral fibers having carcinogenic potential.

When considering these factors, I gave the most weight to the compelling strength of association and consistency, as well as the well-described biologic mechanism.

The currently available scientific research, when considered in its totality, demonstrates a cause and effect relationship between the use of talcum powder products and the development of epithelial ovarian cancer. This opinion is reinforced by my consideration of the Hill factors for the assessment of causation.

In reviewing the scientific and medical literature on talcum powder product use, I also performed a risk assessment and considered whether perineal use of those products poses a safety risk to consumers. This involved careful consideration of the epidemiological literature, data on the dose-response relationship and exposure, as well as the nature of these products, which are used primarily for personal care. I also considered evidence of the toxicity of these products, for which repeated testing and analyses have shown to contain carcinogens.

In considering the weight of this epidemiologic, toxicologic, and mechanistic evidence, across multiple studies, time, demographics, and researchers, demonstrating a consistent association between perineal use of talcum powder products and ovarian cancer, it is my opinion that talcum powder products increase the risk of ovarian cancer and pose a significant health hazard.

In conclusion, it is my opinion that the perineal use of talcum powder products causes ovarian cancer in some users and increases the risk of ovarian cancer in all users of these products.

All of my opinions in this report are provided with respect to a reasonable degree of medical and scientific certainty. I reserve the right to amend or supplement my report as new information becomes available.

References

Acheson ED, G. M. (1982). Mortality of two groups of women who manufactured gas masks from chrysotile and crocidolite asbestos: a 40-year follow-up. *British Journal of Industrial Medicine*, *39*, 344-348.

American Cancer Society. (n.d.). *Key Statistics for Ovarian Cancer*. Retrieved October 31, 2018, from American Cancer Society: https://www.cancer.org/cancer/ovarian-cancer/about/key-statistics.html

American Cancer Society. (n.d.). *What Is Ovarian Cancer?* Retrieved 10 31, 2018, from American Cancer Society: https://www.cancer.org/cancer/ovarian-cancer/about/what-is-ovarian-cancer.html

Balkwill Fran, M. A. (2001). Inflammation and cancer: back to Virchow? *The Lancet*, *357*, 540-545.

Berge W, e. a. (2017). Genital use of talc and risk of ovarian cancer: a meta-analysis. *European Journal of Cancer Prevention*.

Berry G, N. M. (2000). Mortality from all cancers of asbestos factory workers in east London 1933-80. *Occupational and Environmental Medicine*, *57*, 782-785. doi:0.1136/oem.57.11.782

Bertolotti M, F. D. (2008). Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy). *Epidemiol Prev, 32*, 218-228.

Blumenkrantz MJ, G. N. (1981). Retrograde menstruation in women undergoing chronic peritineal dialysis. *57*(5), 667-670.

Booth M, B. V. (1989). Risk factors for ovarian cancer: a case-control study. *British Journal of Cancer, 60*, 592-598.

Buz'Zard AR, L. B. (2007). Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytotherapy Research, 21*, 579-586.

Chang C-J, e. a. (2017). Occupational exposure to talc increases the risk of lung cancer: a meta-analysis of occupational cohort studies. *Canadian Respiratory Journal, 2017*(1270608), 1-12. Retrieved from https://doi.org/10.1155/2017/1270608

Chang S, R. H. (1997). Perineal talc exposure and risk of ovarian carcinoma. *Cancer, 79*, 2396-2401.

Chen Y, W. P. (1992). Risk factors for epithelial ovarian cancer in Beijing, China. *International Journal of Epidemiology, 21*, 23-29.

Cook LS, e. a. (1997). Erratum in "Perineal powder exposure and the risk of ovarian cancer". *American Journal of Epidemiology, 148*, 410.

Cook LS, K. M. (1997). Perineal powder exposure and the risk of ovarian cancer. *American Journal of Epidemiology, 145*, 459-465.

Coussens LM, Z. W. (2002). Inflammation and cancer. *Nature, 420*(6917), 860–867. doi:10.1038/nature01322

Cramer Daniel W, V. A. (2016). The Association Between Talc Use and Ovarian Cancer: A Retrospective Case–Control Study in Two US States. *Epidemiology, 27*, 334-346.

Cramer DW, W. W. (1982). Ovarian cancer and talc: A case-control study. *Cancer, 50*, 372-376.

Egli GE, M. N. (1961). The transport of carbon particles in the human female reproductive tract. *Fertility anfd Sterility, 12*(2), 151-155.

Ferrante D, B. M. (2007). Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato. *Environmental Health Perspectives, 115*, 1401-1405.

Fletcher NM, M. I. (2018). Talcum powder enhances oxidative stress in ovarian cancer cells. *Presented at the 65th meeting of the Society for Reproductive Investigation, San Diego California.*

Fletcher NM, S. G. (2018). Talcum powder enhances cancer antigen 125 in ovarian cancer cells and normal ovarian epithelial cells. *Presented at the 65th meeting of the Society for Reproductive Investigation, San Diego California.*

Fox, A. W. (1982). Mortality of female gas mask assemblers. *British Journal of Industrial Medicine, 39*, 34-38.

Germani D, B. S. (1999). Cohort and mortality study of women compensated for asbestosis in Italy. *American Journal of Industrial Medicine, 36*, 129-134. doi:10.1002/(SICI)1097-0274(199907)36:1<129::AID-AJIM18>3.0.CO;2-9

Halme J, e. a. (1984). Retrograde menstruation in healthy women and in patients with endometriosis. *Obstetrics and Gynecology, 64*(2), 151-154.

Harlow BL, C. D. (1992). Perineal exposure to talc and ovarian cancer risk. *Obstetrics and Gynecology, 80*, 19-26.

Harlow BL, H. P. (1995). A review of perineal talc exposure and risk of ovarian cancer. *Regulatory Toxicology and Pharmacology, 21*, 254-260.

Harlow BL, W. B. (1989). A case–control study of borderline ovarian tumors: the influence of perineal exposure to talc. *American Journal of Epidemiology, 130,* 390-394.

Harper, S. (2019). Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes. *pending publication*.

Hartge P, H. R. (1988). Talc and ovarian cancer [letter]. *JAMA*, *250*, 1844.

Heller DS, W. C. (1996). The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *American Journal of Obstetrics and Gynecology, 174*, 1507-1510.

Henderson WJ, C. J. (1971). Talc and carcinoma of the ovary and cervix. *Journal of Obstetrics and Gynaecology of the British Commonwealth, 78*, 266-272.

Henderson WJ, T. H. (1979). Talc in normal and malignant tissue. *The Lancet*, 499.

Hill, A. (1965). The environment and disease: Association or causation. *Proceedings of the Royal Society of Medicine, 58*(5), 295-300.

International Agency for Research on Cancer. (2010). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 93 - Carbon Black, Titanium Dioxide, and Talc.* Lyon, Freance.

International Agency for Research on Cancer. (2012). Arsenic, Metals, Fibres and Dusts, Vol 100C, A review of human carcinogens. In IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.* Lyon, France: World Health Organization.

Jaiswal M, L. N. (2000). Inflammatory cytokines induce DNA damage and inhibit DNA repair in cholangiocarcinoma cells by a nitric oxide-dependent mechanism. *Cancer Res, 60*, 184-190.

Jurinski JB, R. J. (2001). Biodurability of talc. *American Mineralogist, 86*(4), 392-399.

King, H. M. (n.d.). *Talc: The Softest Mineral*. Retrieved 10 31, 2018, from Geology.com: https://geology.com/minerals/talc.shtml

LA Torre, B. T. (2018). Ovarian Cancer Statistics, 2018. *CA A Cancer Journal for Clinicians, 68*, 284–296.

Langseth H, H. S. (2008). Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health, 62*, 358-360. doi:10.1136/jech.2006.047894

Lockey, J. (1981). Nonasbestos fibrous minerals. *Clinics in Chest Medicine, 2*(2), 203-218.

Longo WE, M. R. (2017). *Analysis of Johnson and Johnson Baby Powder and Valiant Shower To Shower Talc Products for Amphibole (Tremolite) Asbestos: Expert Report.* Materials Analytical Services, LLC, Atlanta .

Magnani C, F. D.-A. (2008). Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occupational and Environmental Medicine, 65*, 164-170. doi:10.1136/oem.2007.032847

Mostafa SAM, e. a. (1985). Foreign body granulomas in normal ovaries. *Obstetrics and Gynecology*, *66*(5), 701-702.

Muscat JE, H. M. (2008). Perineal Talc Use and Ovarian Cancer: A Critical Review. *Eur J Cancer Prev.*, *17*(2), 139-146. doi:10.1097/CEJ.0b013e32811080ef

Nadler DL, I. Z. (2014). Estimating Cancer Latency Times Using a Weibull Model. *Advances in Epidemiology, 2014*, 1-8. doi:10.1155/2014/746769

National Institute for Occupational Safety and Health. (2011). *Asbestos fibers and other elongate mineral particles: State of the science and roadmap for research.* NIOSH Current Intelligence Bulletin No. 62.

National Toxicology Program. (1993). *Toxicology and Carcinogenesis Studies of Talc (CAS No 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3F1 Mice (Inhalation Studies) (1993).* Washington: USDHHS.

Ness Roberta B, C. C. (1999). Possible role of ovarian epithelial inflammation in ovarian cancer. *Journal of the National Cancer Institute, 91*, 1459-1467.

Newhouse ML, B. G. (1972). A study of the mortality of female asbestos workers. *British Journal of Industrial Medicine, 29*, 134-141.

Okada, F. (2007). Beyond foreign-body-induced carcinogenesis: Impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. *International Journal of Cancer*, *121*, 2364–2372.

Paoletti L, S. C. (1984). Evaluation by Electron Microscopy Techniques of Asbestos Contamination in Industrial, Cosmetic, and Pharmaceutical Talcs. *Regulatory Toxicology and Pharmacology*, *4*, 222-235.

Penninkilampi R, E. G. (2018). Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology, 29*, 41-49. doi:10.1097/EDE.0000000000000745

Pira E, P. C. (2005). Cancer mortality in a cohort of asbestos textile workers. *British Journal of Cancer, 92*, 580-586. doi:10.1038/sj.bjc.6602240

Prat, J. (2015). Abridged Republication of FIGO's Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum. *Cancer, 121*, 3452-3454.

Radić I, e. a. (1988). Immunosuppression induced by talc granulomatosis in the rat. *Clin Exp Immunol, 73*, 316-321.

Reid A, H. J. (2008). The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. *Occupational and Environmental Medicine, 65*, 743-749. doi:10.1136/oem.2007.035782

Reid A, S. A. (2009). Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev, 18*, 140-147. doi:10.1158/1055-9965.EPI-08-0746

Rohl AN, e. a. (1976). Consumer talcums and powders: mineral and chemical characterization. *Journal of Toxicology and Environmental Health, 2*, 255-284.

Rohl, A. (1974). Asbestos in talc. *Environmental Health Perspectives, 9,* 129-132.

Rosenblatt KA, S. M. (1992). Mineral fiber exposure and the development of ovarian cancer. *Gynecological Oncology, 45*, 20-25.

Rösler JA, W. H. (1994). Mortality rates in a female cohort following asbestos exposure in Germany. *Journal of Occupational Medicine, 36*, 889–893.

Saed Ghassan M, D. M. (2017). Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecologic Oncology, 145*, 595-604. doi:http://dx.doi.org/10.1016/j.ygyno.2017.02.033

Saed GM, D. M. (2017). Updates on the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecologic Oncology, 145*, 595-602.

Schildkraut JM, A. S.-S. (2016). Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiology, Biomarkers & Prevention, 25*(10), 1411–1417. doi:10.1158/1055-9965.EPI-15-1281

Shukla A, e. a. (2009). Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *American Journal of Respiratory Cell and Molecular Biology, 41*, 114-123.

Sjösten ACE, H. E. (2004). Retrograde migration of glove powder in the human female genital tract. *Human Reproduction, 19*(4), 991-995. doi:10.1093/humrep/deh156

Soong TR, H. B. (2018). Evidence for lineage continuity between early serous proliferations (ESPs) in the Fallopian tube and disseminated high-grade serous carcinomas. *Journal of Pathology, 246*(3), 344-351. doi:10.1002/path.5145

Terry KL, e. a. (2013). Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prevention Research, 6*(8), 811-821.

Torre LA, B. T. (2018). Ovarian Cancer Statistics, 2018. *CA Cancer J Clin, 68*, 284-296.

Trabert, B. (2016). Body Powder and Ovarian Cancer Risk—What Is the Role of Recall Bias? *Cancer Epidemiology, Biomarkers and Prevention, 25*(10), 1369-1370.

Tzonou A, P. A. (1993). Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *International Journal of Cancer, 55*, 408-410.

VanGosen BS, L. H. (2004). *A USGS Study of Talc Deposits and Associated Amphibole Asbestos Within Mined Deposits of the Southern Death Valley Region, California.* United States Geological Survey. Retrieved from https://pubs.usgs.gov/of/2004/1092/

VanOrden D, L. R. (2000). *Weight Percent Compositional Analysis of Seven RTV Talc Samples. Analytical Report to R. T. Vanderbilt Company, Inc. 22 November 2000.* Submitted to Public Comments Record – C. W. Jameson, National Toxicology Program, 10th ROC Nominations "Talc (containing asbestiform fibers)". 4 December 2000., National Toxicology Program.

Venter PF, M. I. (1979). Migration of a particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S Afr Med. J, 55*, 917-919.

Whittemore AS, W. M. (1988). Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *American Journal of Epidemiology, 128*, 1228-1240.

Whysner J, M. M. (2000). Perineal application of talc and cornstarch powders: Evaluation of ovarian cancer risk. *Am J Obstel Gynocol, 182*, 720-724.

Wild, P. (2006). Lung cancer risk and talc not containing asbestiform fibres: a review of the epidemiological evidence. *Occup Environ Med, 63*, 4-9. doi:10.1136/oem.2005.020750

Woodruff, J. (1979). The pathogenesis of ovarian neoplasias. *The Johns Hopkins Medical Journal, 144*(4), 117-120.

Exhibit A

Curriculum Vitae

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Biosketch

Arch "Chip" Carson, MD, PhD is a physician (The Ohio State University), board certified in Occupational Medicine (American Board of Preventive Medicine), who holds a Doctor of Philosophy degree in Toxicology (University of Cincinnati, Kettering Laboratory). He has served on the faculty of the University of Cincinnati and the New York University Medical Center and joined the faculty of the University of Texas School of Public Health in 1992 in its Environmental Sciences Discipline and Occupational and Environmental Health and Aerospace Medicine Module. He is Associate Professor of Occupational Health, directs the Occupational and Environmental Medicine Residency Program and is a member of the research team of the Southwest Center for Occupational and Environmental Health, a NIOSH Education and Research Center, and WHO Collaborating Centre in Occupational Health. He maintains a clinical practice of occupational medicine and medical toxicology. In his more recent role as Medical Director for the University of Texas Medical Branch in Galveston, he is responsible for the health monitoring and care of more than 15,000 employees. He is a frequent consultant to governments, corporations and the legal community on matters related to industrial chemical exposure, toxicology and environmental justice. His research interests include: environmental and occupational chemical exposures, inhalation injuries, metal exposures and cancer, and professional training in occupational medicine.

Professional Activities/Employment

2017-18	University of Texas Medical Branch, Galveston, Assistant Clinical Professor of Preventive Medicine and Family Medicine
2017-18	University of Texas Medical Branch, Galveston, Medical Director, Employee Health Services.
2017-18	Enbridge Corporation, Houston Texas, Medical Director, Employee Health Services.
2010-18	University of Texas Health Science Center, Houston, Associate Professor of Occupational Health.
2010-18	University of Texas Health Science Center at Houston, Program Director, Occupational and Environmental Medicine Residency.
1991-18	Private practice of Occupational Medicine and Toxicology, New York, Texas and Ohio.
2011-18	Spectra Energy Corporation, Houston Texas, Medical Director, Employee Health Services.
1997-13	Texas Medical Center Inc., Houston Texas, Medical Director, Employee Health Services.
1992-08	University of Texas School of Public Health, Assistant Professor of Occupational Medicine and Environmental Sciences.
1998-08	University of Texas Health Science Center at Houston, Program Director, Occupational and Environmental Medicine Residency.
2003-08	Southwest Center for Occupational and Environmental Health, Principal Investigator and Director, Diller Phosgene Exposure Incident Registry of the American Chemistry Council.

2000-06	Chevron Phillips Chemical Company, Houston Texas, Corporate Medical Director.
2003-05	U.S. Department of Energy Office of Worker Advocacy Physician Review Panel Appointee.
1997-04	Southwest Center for Occupational and Environmental Health, Principal Investigator, City of Houston Lead Poisoning Epidemiology Project.
1992-03	UT Health Services, University of Texas Houston Health Science Center, Attending Physician, Occupational Medicine and Toxicology.
1997-01	University of Houston Downtown, Medical Director, Student Health Service.
1998-99	University of Texas School of Public Health, Convener of the Occupational/Environmental Health and Aerospace Medicine Module.
1992-97	Respiratory Consultants of Houston, PA, Attending Physician, Occupational Medicine and Toxicology.
1992-95	Exxon Chemical Americas, Baytown Polymer Center and Basic Chemicals Technology, Baytown TX, Consultant Physician.
1990-91	New York University Medical Center, Bellevue Hospital, Tisch Hospital, and Manhattan VA Hospital, New York NY, Dept. of Medicine, Clinical Instructor.
1982-90	Chemical Information Services Inc, Cincinnati OH, Associate in Toxicology.
1978-87	University of Cincinnati College of Medicine, Cincinnati OH, Instructor and Lecturer, Adjunct Assistant Professor of Industrial Toxicology.
1974-79	University of Cincinnati College of Medicine, Kettering Laboratory, Cincinnati OH, Research Technologist in Occupational Medicine and Clinical Studies.
1969-74	Millstone Inc., Cincinnati OH, Design Engineer, environmental control systems.

Educational Background

2002	Certificate of Board Eligibility, Medical Toxicology, American Board of Preventive Medicine/American Board of Emergency Medicine
1992	Certificate of Training - Residency in Occupational Medicine University of Texas Health Science Center at Houston, School of Public Health, and Southwest Center for Occupational and Environmental Health, Houston TX, 1992.
1991	Certificate of Training - Postgraduate Internship in Internal Medicine, New York University Medical Center and Bellevue Hospital Center, New York NY.
1990	MD - Ohio State University College of Medicine, Columbus OH.
1987	PhD - Kettering Laboratory, University of Cincinnati College of Medicine, Cincinnati OH, awarded in the field of "Environmental Health – Toxicology."
1973	BS - University of Cincinnati College of Arts and Sciences Cincinnati OH. Awarded in "Biological Sciences with Concentration in Engineering."
1969	Rensselaer Polytechnic Institute, Troy NY. Management Engineering
1968	Villa Madonna College, Covington KY. Certificate in Contemporary Physics.

Fellowships

2011-13	UTHealth, Health Educators Fellowship, University of Texas Health Science Center at Houston.

1983-85	American Lung Association Fellowship in Lung Research (Inhalation Toxicology), American Lung Association of Southwestern Ohio, Grant.
1981-82	Owens Corning Fiberglas, Graduate Research Fellowship in Combustion Toxicology.
1979-80	National Institute for Occupational Safety and Health, Centers for Disease Control, Doctoral Fellowship in Industrial Toxicology.

Certifications

2012	License to practice medicine, State of Ohio 35.098635
2010	Certified Healthy Homes Specialist – National Environmental Health Association.
2002	Board Eligibility, Medical Toxicology, American Board of Preventive Medicine/American Board of Emergency Medicine.
1994	Board Certification, Occupational Medicine, American Board of Preventive Medicine.
1992	License to practice medicine, State of Texas J2524.
1991	License to practice medicine, State of New York 186563.
1982	Emergency Hazard Response, Environmental and Industrial Chemical Accident Management, U.S. Environmental Protection Agency.
1979	Pulmonary Function Testing for Occupational Surveillance, NIOSH #003.

Professional Community Service

2013-18	University of Texas Health Science Center at Houston, Steering Committee on Interprofessional Collaboration
2013-18	University of Texas Health Science Center at Houston, Chemical Safety Committee.
1998-18	Association of Environmental and Occupational Clinics/ATSDR community resource on toxic exposures and health consequences, Federal Region VI.
1997-18	City of Houston Biological, Chemical and Radiation Emergency Preparedness Program. Medical Toxicology On-Call Advisor to the Houston Medical Strike Team.
1998-18	Association of Occupational and Environmental Medicine Residency Directors. Chairman 2005-2006
2010-18 1997-08	University of Texas Health Science Center at Houston, Graduate Medical Education Committee
2010-18 1994-08	University of Texas Health Science Center, Houston, Community/Press Resource and Speaker via Public Information Office, (Toxic Exposures and Environmental Health).
1996-18	American College of Occupational and Environmental Medicine, Council on Academic Affairs and Co-chair, Academic Section 2004-2006. Occupational Medicine Residency Directors Committee, Chair 2006-2007, Appointed Member, Taskforce on the Future of Occupational Medicine Education 2005-2007. Appointed Co-chair, Taskforce on the Future of Occupational Medicine Education 2013-2015.
1996-18	Texas College of Occupational and Environmental Medicine. Secretary/Treasurer-2004-5, President Elect-2005-6, President-2006-7, Past President 2007-8.
2003-12	Boy Scouts of America, Sam Houston Council, Registered Adult Leader and Merit Badge Counselor.
2005-08	University of Texas School of Public Health, Practice Council Co-chair

2003-05 U.S. Department of Energy Office of Worker Advocacy Physician Review Panel Appointee.

1996-00 American Public Health Association, Occupational Health Subcommittee

1994-96 Advisory Board, National Environmental Education and Training Center (NEETC), Curriculum Development Committee.

1981-85 Tri-State Air Committee Inc., Cincinnati OH, (voluntary air quality organization) Scientific Advisor, Elected to Board of Directors in 1982, President and Chairman 1984-85.

1981-85 American Lung Association of Southwestern Ohio, Cincinnati OH, (voluntary health organization) speakers bureau.

1982-83 City of Cincinnati, Appointment to Occupational Health Scientific Liaison Board (municipal advisory committee).

1981-83 Cincinnati Area Toxic Substances Coalition, Cincinnati OH, (coalition of business, voluntary, and labor organizations with interest in environmental toxic substance issues) Cofounder and Chairman.

1982-83 Ohio River Valley Committee on Occupational Safety and Health, Cincinnati OH, (organized labor coalition) Scientific Resource Committee.

1972-82 Walnut Hills-Evanston Medical Center, Cincinnati OH, (primary care center) Board of Directors.

Professional Societies

1991-18 American College of Occupational and Environmental Medicine.

1991-18 Texas College of Occupational and Environmental Medicine

2007-18 Texas Public Health Association.

2006-18 International Congress on Occupational Health.

2003-18 American College of Medical Toxicology.

2002-06 Society of Occupational and Environmental Health.

2001-06 American Conference of Governmental Industrial Hygienists.

1994-00 American Public Health Association.

1983-87 American Industrial Hygiene Association.

1983-87 Society of Toxicology.

1980-85 American Thoracic Society, Associate Member and Participant in Occupational and Environment Scientific Session.

Publications

Anderson F, **Carson A**, Whitehead L and Burau K Age, Race and Gender Spatiotemporal Disparities of COPD Emergency Room Visits in Houston, Texas. Occupational Diseases and Environmental Medicine. 3:1-9, 2015. http://dx.doi.org/10.4236/odem.2015.31001.

Anderson F, **Carson A**, Whitehead L and Burau K. Spatiotemporal Analysis of the Effect of Ozone and Fine Particulate on CVD Emergency Room Visits in Harris County, Texas. Open Journal of Air Pollution, 3:87-99, 2014. http://dx.doi.org/10.4236/ojap.2014.34009.

Calcote, JC, **Carson, A**, Peskin, MF, Emery, RJ. An assessment of post-disaster psychological stress in hazardous waste operations and emergency response (HAZWOPER) workers. Disaster Med Public Health Preparedness. 7:452-460, 2013. PMID 24274124.

Delclos GL, Tullis LA, **Carson A**. The services industry. In Occupational and Environmental Lung Diseases. Tarlo SM, Cullinan, Nemery B eds. 2010 pp.258-271. Wiley-Blackwell, West Sussex, UK.

Pugach S, Clarkson T, (**Carson A**). Prenatal mercury exposure and postnatal outcome: clinical case report and analysis. Clin Toxicol 47:366-370, 2009.

Pauluhn J, **Carson A**, Costa DL, Gordon T, Kodavanti U, Last JA, Matthay MA, Pinkerton KE and Sciuto AM. Workshop summary: phosgene-induced pulmonary toxicity revisited: appraisal of early and late markers of pulmonary injury from animal models with emphasis on human significance. Inhalation Toxicology. 19(10):789-810, 2007.

Delclos GL, Gimeno D, Arif AA, Burau KD, **Carson A**, Lusk C, Stock T, Symanski E, Whitehead LW, Zock JP, Benavides FG and Anto JM. Occupational risk factors and asthma among health care professionals, American Journal of Respiratory & Critical Care Medicine. 175(7):667-75, 2007.

Savely SM, **Carson A** and Delclos GL. "A survey of the implementation status of environmental management systems in U.S. colleges and universities" J Cleaner Production, 15(7) 650-659, 2007.

Savely SM, **Carson A** and Delclos GL. "An environmental management system implementation model for U.S. colleges and universities" J Cleaner Production, 15(7) 660-670, 2007.

Delclos GL, Arif AA, Aday L, **Carson A**, Lai D, Lusk C, Stock T, Symanski E, Whitehead LW, Benavides FG and Anto JM. Validation of an asthma questionnaire for use in healthcare workers. Occupational & Environmental Medicine. 63(3):173-9, 2006.

Delclos GL, Bright KA, **Carson A**, Felknor SA, Mackey TA, Morandi MT, Schulze LJH and Whitehead LW. "A global survey of occupational health competencies and curriculum" International Journal of Occupational and Environmental Health; 11:181-194, 2005.

Nooka A, Duonghi L, **Carson A**, Hassan M. Assessing Occupational Risk for Pancreatic Cancer by Chemical Exposures and Work History: A Case-Control study at MD Anderson Cancer Center. American Association for Cancer Research, Orlando. March, 2004.

Mitchell CS, Moline J, Avery AN, Baker D, Blessman JE, **Carson A**, Cosby O, Darcey D, Ducatman A, Emmett EA, Forst L, Gerr F, Gochfeld M, Guidotti TL, Harber P, Hu H, Hegmann KT, Kipen HM, Levin J, McGrail MP, Meyer JD, Mueller KL, Prince S, Rubin R, Schwerha JJ, Sprince NL, Taiwo O and Upfal M. In response to the 2002, vol. 22, no. 4 article entitled "The rise and fall of occupational medicine in the United States" [Letter] Am J Preventive Med. 23(4):307-9, 2002.

Carson A and Delclos GL. "The Respiratory System," in Modern Industrial Hygiene: Volume II – Biological Aspects, JL Perkins, ed. 2003, American Conference of Governmental Industrial Hygienists, Cincinnati.

Carson A, Colombo S and Alavi. A, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, March 31, 2000, Technical Report (Principal Investigator).

Townsend MC, Lockey JE, Velez H, **Carson A**, Cowl CT, Delclos GL, Gerstenhaber BJ, Harber PI, Horvath EP, Jolly AT, Jones SH, Knackmuhs GG, Lindesmith LA, Markham TN, Raymond LW, Rosenberg DM, Sherson D, Smith DD, and Wintermeyer SF. ACOEM Position Statement – "Spirometry in the Occupational Setting" JOEM; 42: 228-245, 2000.

Bright K, Delclos G, **Carson A**, Felknor S, Mackey T, Morandi M, Schultz L and Whitehead L. A Global Study of Occupational Health Competencies and Curricula, Report to the World Health Organization, March, 2000, Southwest Center for Occupational and Environmental Health.

Carson A, Guevara E, Delclos GL, Murray KA, Burau KD, Morandi MT, Felknor SA, ("A Study of General Health of Workers of the Industrial Complex of Barrancabermeja") in [Compendium on Occupational Health in the Petroleum Industry of Colombia: Technical and Scientific Report of the "Occupational Health in the Petroleum Industry" Project], 1999 Pan American Health Organization (co-author).

Carson A, Hangoc V and Bahrainwala M, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1999, Technical Report (Principal Investigator).

Carson A, Spears B, and Burau K, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1998, Technical Report (Principal Investigator).

Carson A, Detry M, Spears B, and Burau K, City of Houston Childhood Lead Poisoning Prevention Program: Case Density and Impact Analysis, June 30, 1997, Technical Report (Principal Investigator).

Delclos GL and **Carson A**, "Acute Gaseous Exposures," in Occupational and Environmental Respiratory Diseases, P Harber, M Schenker, and J Balmes eds. 1995, Mosby Yearbook Pub., St. Louis.

Carson A, "Respiratory Effects of Exposure to Fresh Smokes from Pyrolytic Decomposition of Styrene Plastic in Rats." Doctoral Dissertation, University of Cincinnati Kettering Laboratory, 1987.

Carson A, "A Dynamic Method for the Generation of Fresh Smokes From Combustion or Pyrolytic Decomposition of Structural Materials." Doctoral Dissertation, University of Cincinnati Kettering Laboratory, 1987.

Samuels SJ, Lemasters GK and **Carson A**, "Statistical Methods for Describing Occupational Exposure Measurements," Am. Ind. Hyg. Assoc. J., 46:427-433, 1985.

Lemasters GK, **Carson A** and Samuels SJ, "Occupational Styrene Exposure for Twelve Product Categories in the Reinforced-Plastics Industry," Am. Ind. Hyg. Assoc. J., 46:434-441, 1985.

Lockey JE, Brooks SM, Jarabek AM, Khoury PR, McKay RT, **Carson A**, Morrison JA, Wiot JF and Spitz HB. "Pulmonary changes after exposure to vermiculite contaminated with fibrous tremolite" Am Rev Respir Dis. 129(6):952-8, 1984.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P, Khoury P, Morrison J, Wiot J, Spitz H and Brooks SM, "Pulmonary Hazards from Vermiculite," in Health Issues Related to Metal and Nonmetallic Mining, WL Wagner, W Rom and P Merchant eds. 1983, Butterworth's, Boston.

Vinegar A and **Carson A**, "Pulmonary Function Changes in Chinese Hamsters Exposed Six Months to Diesel Exhaust," Environ Int, 5:369-371, 1981.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P,. Khoury P, Morrison J, Prior J and Brooks SM, "Health Effects of Vermiculite Exposure," Am Rev Respir Dis, 123:133, 1981 abstract.

Lockey JE, Jarabek A, **Carson A**, McKay R, Harber P, Khoury P, Morrison J and Brooks SM, "Single-Breath Diffusing Capacity (DLCOsb) in a Working Population," Am Rev Respir Dis, 123:132, 1981 abstract.

Vinegar A, **Carson A** and Pepelko WE, "Pulmonary Function Changes in Chinese Hamsters Exposed to Diesel Exhaust," in Health Effects of Diesel Engine Emissions, Vol. 2, WE Pepelko, RM Danner and NA Clarke eds, 1980, US Environmental Protection Agency, Washington.

Carson A, Vinegar A, Leng J and Cooper G, "Effects of Chronic Exposure to some Diesel Exhaust Components on Lung Function in Rats," Fed Proc, 39:1091, 1980 abstract.

Elia VJ, Anderson LA, MacDonald TJ, **Carson A**, Buncher CR and Brooks SM, "Determination of Urinary Mandelic and Phenylglyoxylic Acids in Styrene Exposed Workers and a Control Population," Am Ind Hyg Assoc J, 41:922-926, 1980.

Brooks SM, Anderson LA, Emmett E, **Carson A**, Tsay JY, Elia VJ, Buncher CR and Karbowsky R, "The Effects of Protective Equipment on Styrene Exposure in Workers in the Reinforced Plastics Industry," Arch Environ Health, 35:287-294, 1980.

Brooks SM, Zipp T, Barber M and **Carson A**, "Measurement of Maximal Expiratory Flow Rates in Cigarette Smokers Using Gases of High and Low Densities," Am Rev Respir Dis, 118:75-81, 1978.

Exhibit B

LITERATURE:

"A Survey of the Long-Term Effects of Talc and Kaolin Pleurodesis." *British Journal of Diseases of the Chest* 73 (1979): 285–88.

Acencio, Milena M. P., Evaldo Marchi, Lisete R. Teixeira, Bruna Rocha Silva, Juliana Sanchez Silva, Carlos Sergio Rocha Silva, Vanessa Adelia Alvarenga, Leila Antonangelo, Francisco Suso Vargas, and Vera Luiza Capelozzi. "Talc Particles and Pleural Mesothelium Interface Modulate Apoptosis and Inflammation." *Pathology* 46, no. S2 (2014): S76.

ACGIH. Product: Asbestos: TLV(R) Chemical Substances 7th Edition Documentation. Accessed August 16, 2018.

ACGIH. 2017 TLVs and BEIs: ACGIH. Accessed August 16, 2018.

Acheson, E D, M J Gardner, E C Pippard, and L P Grime. "Mortality of Two Groups of Women Who Manufactured Gas Masks from Chrysotile and Crocidolite Asbestos: A 40-Year Follow-Up." *British Journal of Industrial Medicine* 39, no. 4 (November 1982): 344–48.

Akhtar, Mohd Javed, Maqusood Ahamed, M.A. Majeed Khan, Salman A. Alrokayan, Iqbal Ahmad, and Sudhir Kumar. "Cytotoxicity and Apoptosis Induction by Nanoscale Talc Particles from Two Different Geographical Regions in Human Lung Epithelial Cells." *Environmental Toxicology* 29 (2014): 394–406.

Akhtar, Mohd Javed, Sudhir Kumar, Ramesh Chandra Murthy, Mohd Ashquin, Mohd Imran Khan, Govil Patil, and Iqbal Ahmad. "The Primary Role of Iron-Mediated Lipid Peroxidation in the Differential Cytotoxicity Caused by Two Varieties of Talc Nanoparticles on A549 Cells and Lipid Peroxidation Inhibitory Effect Exerted by Ascorbic Acid." *Toxicology in Vitro: An International Journal Published in Association with BIBRA* 24, no. 4 (June 2010): 1139–47.

American Cancer Society. "Key Statistics for Ovarian Cancer."

American Cancer Society. "What Is Ovarian Cancer?,"

Anderson, Garnet L., Howard L. Judd, Andrew M. Kaunitz, David H. Barad, Shirley A. A. Beresford, Mary Pettinger, James Liu, S. Gene McNeeley, Ana Maria Lopez, and Women's Health Initiative Investigators. "Effects of Estrogen plus Progestin on Gynecologic Cancers and Associated Diagnostic Procedures: The Women's Health Initiative Randomized Trial." *JAMA* 290, no. 13 (October 1, 2003): 1739–48.

Antoniou, A., P. D. P. Pharoah, S. Narod, H. A. Risch, J. E. Eyfjord, J. L. Hopper, N. Loman, et al. "Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 Mutations Detected in Case Series Unselected for Family History: A Combined Analysis of 22 Studies." *American Journal of Human Genetics* 72, no. 5 (May 2003): 1117–30.

Arellano-Orden, Elena, Auxiliadora Romero-Falcon, Jose Martin Juan, Manuel Ocana Jurado, Francisco Rodriguez-Panadero, and Ana Montes-Worboys. "Small Particle-Size Talc Is Associated with Poor Outcome and Increased Inflammation in Thoracoscopic Pleurodesis." *Respiration* 86 (2013): 201–9.

Armstrong, Deborah K., Brian Bundy, Lari Wenzel, Helen Q. Huang, Rebecca Baergen, Shashikant Lele, Larry J. Copeland, Joan L. Walker, Robert A. Burger, and Gynecologic Oncology Group. "Intraperitoneal Cisplatin and Paclitaxel in Ovarian Cancer." *The New England Journal of Medicine* 354, no. 1 (January 5, 2006): 34–43.

"ATSDR - Toxicological Profile: Asbestos." Accessed August 16, 2018.

Baldwin, Lauren A., Bin Huang, Rachel W. Miller, Thomas Tucker, Scott T. Goodrich, Iwona

Podzielinski, Christopher P. DeSimone, Fred R. Ueland, John R. van Nagell, and Leigh G. Seamon. "Ten-Year Relative Survival for Epithelial Ovarian Cancer:" *Obstetrics & Gynecology* 120, no. 3 (September 2012): 612–18.

Balkwill, Fran, and Alberto Mantovani. "Inflammation and Cancer: Back to Virchow?" *The Lancet* 357, no. 9255 (February 2001): 539–45.

Bartrip, P.W. "History of Asbestos Related Disease." *Postgrad Med J* 80 (2004): 72–76.

Beck, B. D., H. A. Feldman, J. D. Brain, T. J. Smith, M. Hallock, and B. Gerson. "The Pulmonary Toxicity of Talc and Granite Dust as Estimated from an in Vivo Hamster Bioassay." *Toxicology and Applied Pharmacology* 87, no. 2 (February 1987): 222–34.

Begg, Melissa D., and Dana March. "Cause and Association: Missing the Forest for the Trees." *American Journal of Public Health* 108, no. 5 (May 2018): 620.

Belotte, Jimmy, Nicole M. Fletcher, Awoniyi O. Awonuga, Mitchell Alexis, Husam M. Abu-Soud, Ghassan M. Saed, Michael P. Diamond, and Mohammed G. Saed. "The Role of Oxidative Stress in the Development of Cisplatin Resistance in Epithelial Ovarian Cancer." *Reproductive Sciences* 21, no. 4 (2014): 503–8.

Belotte, Jimmy, Nicole M. Fletcher, Mohammed G. Saed, Mohammed S. Abusamaan, Gregory Dyson, Michael P. Diamond, and Ghassan M. Saed. "A Single Nucleotide Polymorphism in Catalase Is Strongly Associated with Ovarian Cancer Survival." *PloS One* 10, no. 8 (2015).

Berge, Wera, Kenneth Mundt, Hung Luu, and Paolo Boffetta. "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention*, January 2017, 1.

Berge. "Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis." *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 27, no. 3 (2018): 248–57.

Berry, G., M. L. Newhouse, and J. C. Wagner. "Mortality from All Cancers of Asbestos Factory Workers in East London 1933-80." *Occupational and Environmental Medicine* 57, no. 11 (November 2000): 782–85.

Bertolotti, Marinella, Daniela Ferrante, Dario Mirabelli, Mario Botta, Marinella Nonnato, Annalisa Todesco, Benedetto Terracini, and Corrado Magnani. "[Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy)]." *Epidemiologia E Prevenzione* 32, no. 4–5 (October 2008): 218–28.

Blank, M M, N Wentzensen, M A Murphy, A Hollenbeck, and Y Park. "Dietary Fat Intake and Risk of Ovarian Cancer in the NIH-AARP Diet and Health Study." *British Journal of Cancer* 106, no. 3 (January 31, 2012): 596–602.

Blejer, H. and Robert Arlon. "Talc: A Possible Occupational and Environmental Carcinogen." *Journal of Occupational Medicine* No. 15(2) (February 1973): 92-97.

Blount, A M. "Amphibole Content of Cosmetic and Pharmaceutical Talcs." *Environmental Health Perspectives* 94 (August 1991): 225–30.

Bluemel, Piza, and Zischka-Konorsa, W. "Animal experimental investigations of tissue reactions to starch and talcum powder after intraperitoneal application." *Wiener klinische Wochenschrift* 74, no. 1 (January 1962).

Blumenkrantz, M. J., N. Gallagher, R. A. Bashore, and H. Tenckhoff. "Retrograde Menstruation in Women Undergoing Chronic Peritoneal Dialysis." *Obstetrics and Gynecology* 57, no. 5 (May 1981): 667–70.

Boorman, G. A., and J. C. Seely. "The Lack of an Ovarian Effect of Lifetime Talc Exposure in

F344/N Rats and B6C3F1 Mice." *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 242–43.

Booth, M., V. Beral, and P. Smith. "Risk Factors for Ovarian Cancer: A Case-Control Study." *British Journal of Cancer* 60, no. 4 (October 1989): 592–98.

Bottazzi, Barbara, Elio Riboli, and Alberto Mantovani. "Aging, Inflammation and Cancer." *Seminars in Immunology*, November 5, 2018.

Brand, K.G., Lance C. Buoen, Kenneth H. Johnson, and Inge Brand. "Etiological Factors, Stages, and the Role of the Foreign Body in Foreign Body Tumorigenesis: A Review." *Cancer Research* No. 35 (February 1975): 279-286.

Brand, K.G. "Cancer Associated with Asbestosis, Schistosomiasis, Foreign Bodies, and Scars." *Cancer: A Comprehensive Treatise* 2nd Edition. Etiology: Chemical and Physical Carcinogenesis. Plenum Press. (1982).

Brand, K.G. "Solid State Carcinogenesis." *Barbury Report 25: Nongenotoxic Mechanisms in Carcinogensis.* (1987).

Brodeur, Paul. "The Magic Mineral." *The New Yorker* October 12, 1968.

Bunderson-Schelvan, Melisa, Jean C. Pfau, Robert Crouch, and Andrij Holian. "Nonpulmonary Outcomes of Asbestos Exposure." *Journal of Toxicology and Environmental Health. Part B, Critical Reviews* 14, no. 1–4 (2011): 122–52.

Burn, John, Anne-Marie Gerdes, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Moeslein, Sylviane Olschwang, Diane Eccles, et al. "Long-Term Effect of Aspirin on Cancer Risk in Carriers of Hereditary Colorectal Cancer: An Analysis from the CAPP2 Randomised Controlled Trial." *Lancet (London, England)* 378, no. 9809 (December 17, 2011): 2081–87.

Butterworth, B.E., J.A.A Popp, R.B. Connolly and T.L. Goldsworthy. "Chemically Induced Cell Proliferation in Carcinogenesis." *Mechanisms of Carcinogenesis in Risk Identification.* (1992): 279-305.

Buz'Zard, Amber R., and Benjamin H. S. Lau. "Pycnogenol® Reduces Talc-Induced Neoplastic Transformation in Human Ovarian Cell Cultures." *Phytotherapy Research* 21, no. 6 (June 2007): 579–86.

Caldwell, Carlyle G., White Thomas Aubrey, William L. George, and James J. Eberl. Medical dusting powder. United States US2626257A, filed May 21, 1952, and issued January 20, 1953.

Camargo, M. Constanza, Leslie T. Stayner, Kurt Straif, Margarita Reina, Umaima Al-Alem, Paul A. Demers, and Philip J. Landrigan. "Occupational Exposure to Asbestos and Ovarian Cancer: A Meta-Analysis." *Environmental Health Perspectives* 119, no. 9 (September 2011): 1211–17.

Carr, C.J. "Talc: Consumer Uses and Health Perspectives" 21 (1995): 211–15.

Chan, Andrew T., Edward L. Giovannucci, Jeffrey A. Meyerhardt, Eva S. Schernhammer, Gary C. Curhan, and Charles S. Fuchs. "Long-Term Use of Aspirin and Nonsteroidal Anti-Inflammatory Drugs and Risk of Colorectal Cancer." *JAMA* 294, no. 8 (August 24, 2005): 914–23.

Chang, Che-Jui, Yu-Kang Tu, Pau-Chung Chen, and Hsiao-Yu Yang. "Occupational Exposure to Talc Increases the Risk of Lung Cancer: A Meta-Analysis of Occupational Cohort Studies." *Canadian Respiratory Journal*, 2017.

Chang, Stella, and Harvey A. Risch. "Perineal Talc Exposure and Risk of Ovarian Carcinoma." *Cancer* 79, no. 12 (June 15, 1997): 2396–2401.

Chen, F., K. Gaitskell, M. J. Garcia, A. Albukhari, J. Tsaltas, and A. A. Ahmed. "Serous Tubal Intraepithelial Carcinomas Associated with High-Grade Serous Ovarian Carcinomas: A Systematic Review." *BJOG: An International Journal of Obstetrics and Gynaecology* 124, no. 6 (May 2017): 872–78.

Chen, Lee-May, and Jonathan S Berek. "Overview of Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum." *UpToDate*, 2018.

Chen, L-M, et al. "Epithelial Carcinoma of the Ovary, Fallopian Tube, and Peritoneum: Epidemiology and Risk Factors - UpToDate," 2018.

Chen, Xi, Gerd A. Müller, Marianne Quaas, Martin Fischer, Namshik Han, Benjamin Stutchbury, Andrew D. Sharrocks, and Kurt Engeland. "The Forkhead Transcription Factor FOXM1 Controls Cell Cycle-Dependent Gene Expression through an Atypical Chromatin Binding Mechanism." *Molecular and Cellular Biology* 33, no. 2 (January 2013): 227–36.

Chen, Y., P. C. Wu, J. H. Lang, W. J. Ge, P. Hartge, and L. A. Brinton. "Risk Factors for Epithelial Ovarian Cancer in Beijing, China." *International Journal of Epidemiology* 21, no. 1 (February 1992): 23–29.

Chien, Jeremy, Hugues Sicotte, Jian-Bing Fan, Sean Humphray, Julie M. Cunningham, Kimberly R. Kalli, Ann L. Oberg, et al. "TP53 Mutations, Tetraploidy and Homologous Recombination Repair Defects in Early Stage High-Grade Serous Ovarian Cancer." *Nucleic Acids Research* 43, no. 14 (August 18, 2015): 6945–58.

Chittenden, B. G., G. Fullerton, A. Maheshwari, and S. Bhattacharya. "Polycystic Ovary Syndrome and the Risk of Gynaecological Cancer: A Systematic Review." *Reproductive Biomedicine Online* 19, no. 3 (September 2009): 398–405.

Cibula, D., M. Widschwendter, O. Májek, and L. Dusek. "Tubal Ligation and the Risk of Ovarian Cancer: Review and Meta-Analysis." *Human Reproduction Update* 17, no. 1 (January 1, 2011): 55–67.

Cibula, David, Martin Widschwendter, Michael Zikan, and Ladislav Dusek. "Underlying Mechanisms of Ovarian Cancer Risk Reduction after Tubal Ligation." *Acta Obstetricia Et Gynecologica Scandinavica* 90, no. 6 (June 2011): 559–63.

CIMBA, Georgia Chenevix-Trench, Roger L Milne, Antonis C Antoniou, Fergus J Couch, Douglas F Easton, and David E Goldgar. "An International Initiative to Identify Genetic Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: The Consortium of Investigators of Modifiers of BRCA1 and BRCA2 (CIMBA)." *Breast Cancer Research* 9, no. 2 (December 2007).

Cohen, Samuel M., and Lora L. Arnold. "Chemical Carcinogenesis." *Toxicological Sciences* 120, no. suppl_1 (March 1, 2011): S76–92.

Colditz, Graham A. "Cancer Prevention." *UpToDate*, 2018.

Collaborative Group on Epidemiological Studies of Ovarian Cancer, V. Beral, R. Doll, C. Hermon, R. Peto, and G. Reeves. "Ovarian Cancer and Oral Contraceptives: Collaborative Reanalysis of Data from 45 Epidemiological Studies Including 23,257 Women with Ovarian Cancer and 87,303 Controls." *Lancet* 371, no. 9609 (January 26, 2008): 303–14.

Collaborative Group On Epidemiological Studies Of Ovarian Cancer, V. Beral, K. Gaitskell, C. Hermon, K. Moser, G. Reeves, and R. Peto. "Menopausal Hormone Use and Ovarian Cancer Risk: Individual Participant Meta-Analysis of 52 Epidemiological Studies." *Lancet (London, England)* 385, no. 9980 (May 9, 2015): 1835–42.

Committee on Practice Bulletins–Gynecology, Committee on Genetics, Society of Gynecologic Oncology. "Practice Bulletin No 182: Hereditary Breast and Ovarian Cancer Syndrome." *Obstetrics and Gynecology* 130, no. 3 (2017): e110–26.

Compton, Sarah A., Sezgin Ozgür, and Jack D. Griffith. "Ring-Shaped Rad51 Paralog Protein Complexes Bind Holliday Junctions and Replication Forks as Visualized by Electron Microscopy." *The Journal of Biological Chemistry* 285, no. 18 (April 30, 2010): 13349–56.

Cook, Linda S., Mary L. Kamb, and Noel S. Weiss. "Perineal Powder Exposure and the Risk of Ovarian Cancer." *American Journal of Epidemiology* 145, no. 5 (March 1, 1997): 459–65.

Cook, LS. "Erratum in 'Perineal Powder Exposure and the Risk of Ovarian Cancer'." *American Journal of Epidemiology* 148, no. 410 (1997).

Coussens, Lisa M., and Zena Werb. "Inflammation and Cancer." *Nature* 420, no. 6917 (December 19, 2002): 860–67.

Cralley, L. J., M. M. Key, D. H. Groth, W. S. Lainhart, and R. M. Ligo. "Fibrous and Mineral Content of Cosmetic Talcum Products." *American Industrial Hygiene Association Journal* 29, no. 4 (August 1968): 350–54.

Cramer, D. W. "Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study." *Obstetrics and Gynecology* 94, no. 1 (July 1999): 160–61.

Cramer, D. W., R. F. Liberman, L. Titus-Ernstoff, W. R. Welch, E. R. Greenberg, J. A. Baron, and B. L. Harlow. "Genital Talc Exposure and Risk of Ovarian Cancer." *International Journal of Cancer. Journal International Du Cancer* 81, no. 3 (May 5, 1999): 351–56.

Cramer, D. W., W. R. Welch, R. E. Scully, and C. A. Wojciechowski. "Ovarian Cancer and Talc: A Case-Control Study." *Cancer* 50, no. 2 (July 15, 1982): 372–76.

Cramer, Daniel W., Linda Titus-Ernstoff, John R. McKolanis, William R. Welch, Allison F. Vitonis, Ross S. Berkowitz, and Olivera J. Finn. "Conditions Associated with Antibodies Against the Tumor-Associated Antigen MUC1 and Their Relationship to Risk for Ovarian Cancer." *Cancer Epidemiology Biomarkers & Prevention* 14, no. 5 (May 1, 2005): 1125–31.

Cramer, Daniel W., Allison F. Vitonis, Kathryn L. Terry, William R. Welch, and Linda J. Titus. "The Association between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States." *Epidemiology (Cambridge, Mass.)*, December 17, 2015.

Cramer, Daniel, et al. "The Association Between Talc Use and Ovarian Cancer: A Retrospective Case-Control Study in Two US States." *Epidemiology (Cambridge, Mass.)* 27, no. 3 (May 2016): 334–46.

Cramer, Daniel W., William R. Welch, Ross S. Berkowitz, and John J. Godleski. "Presence of Talc in Pelvic Lymph Nodes of a Woman with Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc." *Obstetrics and Gynecology* 110, no. 2 Pt 2 (August 2007): 498–501.

Cramer, Daniel W., William R. Welch, Robert E. Scully, and Carol A. Wojciechowski. "Ovarian Cancer and Talc. A Case-Control Study." *Cancer* 50, no. 2 (July 15, 1982): 372–76.

Crum, Christopher P, Jonathan Bijron, and Brooke E. Howitt. "Pathogenesis of Ovarian, Fallopian Tubal, and Peritoneal Serous Carcinomas." *UpToDate*, 2018.

Crusz, Shanthini M., and Frances R Balkwill. "Inflammation and Cancer: Advances and New Agents." *Nature Reviews Clinical Oncology* 12 (October 2015): 584–96.

Curtis D. Klaassen, and John Doull. *Casarett and Doull's Toxicology : The Basic Science of*

Poisons. 8th Edition. McGraw-Hill Education, 2013.
Danforth, Kim N., Shelley S. Tworoger, Jonathan L. Hecht, Bernard A. Rosner, Graham A. Colditz, and Susan E. Hankinson. "Breastfeeding and Risk of Ovarian Cancer in Two Prospective Cohorts." *Cancer Causes & Control: CCC* 18, no. 5 (June 2007): 517–23.
Demirer, Ersin, Christian F. Ghattas, Mohamed O. Radwan, and Elamin M. Elamin. "Clinical and Prognostic Features of Erionite-Induced Malignant Mesothelioma." *Yonsei Med J* 56(2) (2015): 311-323.
Devaja, Omer. *Ovarian Cancer From Pathogenesis to Treatment*. IntechOpen, 2018.
Ding, Yuan C., Lesley McGuffog, Sue Healey, Eitan Friedman, Yael Laitman, Shani-Paluch-Shimon, Bella Kaufman, et al. "A Nonsynonymous Polymorphism in IRS1 Modifies Risk of Developing Breast and Ovarian Cancers in BRCA1 and Ovarian Cancer in BRCA2 Mutation Carriers." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 21, no. 8 (August 2012): 1362–70.
Dixon, Suzanne C., Christina M. Nagle, Nicolas Wentzensen, Britton Trabert, Alicia Beeghly-Fadiel, Joellen M. Schildkraut, Kirsten B. Moysich, et al. "Use of Common Analgesic Medications and Ovarian Cancer Survival: Results from a Pooled Analysis in the Ovarian Cancer Association Consortium." *British Journal of Cancer* 116, no. 9 (April 25, 2017): 1223–28. https://doi.org/10.1038/bjc.2017.68.
Dodson, R. F., M. O'Sullivan, C. J. Corn, and S. P. Hammar. "Quantitative Comparison of Asbestos and Talc Bodies in an Individual with Mixed Exposure." *American Journal of Industrial Medicine* 27, no. 2 (February 1995): 207–15.
Donaldson, Ken. "The Inhalation Toxicology of *p*-aramid Fibrils." *Critical Reviews in Toxicology*, No. 39(6) (2009): 487-500.
Donaldson, Ken, Fiona A. Murphy, Rodger Duffin, Craig A. Poland. "Asbestos, Carbon Nanotubes and the Pleural Mesothelium: A Review of the Hypothesis Regarding the Role of Long Fibre Retention in the Parietal Pleura, Inflammation and Mesothelioma." *Particle and Fibre Toxicology* No. 7 (2010): 5.
D.R. Petterson. "JNJ 000251888," April 26, 1973.
Dubeau, L., and R. Drapkin. "Coming into Focus: The Nonovarian Origins of Ovarian Cancer." *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 24 Suppl 8 (November 2013): viii28–35. https://doi.org/10.1093/annonc/mdt308.
Eberl, J. J., and W. L. George. "Comparative Evaluation of the Effects of Talcum and a New Absorbable Substitute on Surgical Gloves." *American Journal of Surgery* 75, no. 3 (March 1948): 493–97.
Egli, G. E., and M. Newton. "The Transport of Carbon Particles in the Human Female Reproductive Tract." *Fertility and Sterility* 12 (April 1961): 151–55.
Eng, Kevin H., J. Brian Szender, John Lewis Etter, Jasmine Kaur, Samantha Poblete, Ruea-Yea Huang, Qianqian Zhu, et al. "Paternal Lineage Early Onset Hereditary Ovarian Cancers: A Familial Ovarian Cancer Registry Study." *PLoS Genetics* 14, no. 2 (February 2018): e1007194. https://doi.org/10.1371/journal.pgen.1007194.
"Expert Report of Michael Crowley, Ph.D., In Re: Talcum Powder Prod. Liab. Litig., MDL No. 2738," November 12, 2018.
Fasching, Peter A., Simon Gayther, Leigh Pearce, Joellen M. Schildkraut, Ellen Goode, Falk Thiel, Georgia Chenevix-Trench, et al. "Role of Genetic Polymorphisms and Ovarian Cancer Susceptibility." *Molecular Oncology* 3, no. 2 (April 2009): 171–81.

https://doi.org/10.1016/j.molonc.2009.01.008.
Fathalla, M. F. "Incessant Ovulation and Ovarian Cancer - a Hypothesis Re-Visited." *Facts, Views & Vision in ObGyn* 5, no. 4 (2013): 292–97.
Fathalla, M. F. "Incessant Ovulation--a Factor in Ovarian Neoplasia?" *Lancet* 2, no. 7716 (July 17, 1971): 163.
FDA. "Ltr to Samuel S. Epstein, M.D., RE: Docket Numbers 94P-0420 and FDA-2008-P-0309-0001 /CP," April 1, 2017.
Fedak, Kristen M., Autumn Bernal, Zachary A. Capshaw, and Sherilyn Gross. "Applying the Bradford Hill Criteria in the 21st Century: How Data Integration Has Changed Causal Inference in Molecular Epidemiology." *Emerging Themes in Epidemiology* 12, no. 14 (2015).
"Federal Register Vol. 81, No.243, December 19, 2016 FDA Ban on Surgical Gloves." Accessed August 16, 2018.
Ferguson, Lynnette R. "Chronic Inflammation and Mutagenesis." *Mutation Research* 690, no. 1–2 (August 7, 2010): 3–11.
Fernandes, José Veríssimo, Ricardo Ney Oliveira Cobucci, Carlos André Nunes Jatobá, Thales Allyrio Araújo de Medeiros Fernandes, Judson Welber Veríssimo de Azevedo, and Josélio Maria Galvão de Araújo. "The Role of the Mediators of Inflammation in Cancer Development." *Pathology & Oncology Research* 21, no. 3 (July 2015): 527–34.
Ferrante, Daniela, Marinella Bertolotti, Annalisa Todesco, Dario Mirabelli, Benedetto Terracini, and Corrado Magnani. "Cancer Mortality and Incidence of Mesothelioma in a Cohort of Wives of Asbestos Workers in Casale Monferrato, Italy." *Environmental Health Perspectives* 115, no. 10 (October 2007): 1401–5.
Ferrer, Jaume, Juan F. Montes, Maria A. Villarino, Richard W. Light, and José García-Valero. "Influence of Particle Size on Extrapleural Talc Dissemination after Talc Slurry Pleurodesis." *Chest* 122, no. 3 (September 2002): 1018–27.
Fields, L., et al. "Gynecologic Cancer." Excerpt. *Clinical Oncology* 2001.
Fiume, Monice M., Ivan Boyer, Wilma F. Bergfeld, Donald V. Belsito, Ronald A. Hill, Curtis D. Klaassen, Daniel C. Liebler, et al. "Safety Assessment of Talc as Used in Cosmetics." *International Journal of Toxicology* 34, no. 1 suppl (July 1, 2015): 66S-129S.
Fletcher, Nicole M., Jimmy Belotte, Mohammed G. Saed, Ira Memaj, Michael P. Diamond, Robert T. Morris, and Ghassan M. Saed. "Specific Point Mutations in Key Redox Enzymes Are Associated with Chemoresistance in Epithelial Ovarian Cancer." *Free Radical Biology and Medicine* 102 (2017): 122–32.
Fletcher, Nicole M., Zhongliang Jiang, Rouba Ali-Fehmi, Nancy K. Levin, Jimmy Belotte, Michael A. Tainsky, Michael P. Diamond, Husam M. Abu-Soud, and Ghassan M. Saed. "Myeloperoxidase and Free Iron Levels: Potential Biomarkers for Early Detection and Prognosis of Ovarian Cancer." *Cancer Biomarkers* 10 (2012 2011): 267–75.
Fletcher, Nicole, Memaj, Ira, and Saed, Ghassan. "Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells." *Reproductive Sciences*, February 28, 2018.
Fletcher, NM, and GM Saed. "Talcum Powder Enhances Cancer Antigen 125 Levels in Ovarian Cancer Cells." *Presented at the 65th Meeting of the Society for Reproductive Investigation, San Diego, California*, 2018.
Folkins, Ann K., Elke A. Jarboe, Jonathan L. Hecht, Michael G. Muto, and Christopher P. Crum. "Chapter 24 - Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy." In *Diagnostic Gynecologic and Obstetric Pathology (Third Edition),*

844–64. Philadelphia: Content Repository, 2018.

Ford, D., D.F. Easton, M. Stratton, S. Narod, D. Goldgar, P. Devilee, D.T. Bishop, et al. “Genetic Heterogeneity and Penetrance Analysis of the BRCA1 and BRCA2 Genes in Breast Cancer Families.” *The American Journal of Human Genetics* 62, no. 3 (March 1998): 676–89.

Frank, Czul and Lascano Jorge. “An Uncommon Hazard: Pulmonary Talcosis as a Result of Recurrent Aspiration of Baby Powder.” *Respiratory Medicine CME* No. 4 (2011): 109-111.

Freedman, Ralph S, Michael Deavers, Jinsong Liu, and Ena Wang. “Peritoneal Inflammation – A Microenvironment for Epithelial Ovarian Cancer (EOC).” *Journal of Translational Medicine* 2, no. 23 (2004).

Friebel, Tara M., Susan M. Domchek, and Timothy R. Rebbeck. “Modifiers of Cancer Risk in BRCA1 and BRCA2 Mutation Carriers: Systematic Review and Meta-Analysis.” *Journal of the National Cancer Institute* 106, no. 6 (June 2014): dju091.

Frost, G. “The Latency Period of Mesothelioma among a Cohort of British Asbestos Workers (1978-2005).” *British Journal of Cancer* 109, no. 7 (October 1, 2013): 1965–73.

Galea, Sandro, and Roger D. Vaughan. “Moving Beyond the Cause Constraint: A Public Health of Consequence, May 2018.” *American Journal of Public Health* 108, no. 5 (May 2018): 602–3.

Gates, Margaret A., Bernard A. Rosner, Jonathan L. Hecht, and Shelley S. Tworoger. “Risk Factors for Epithelial Ovarian Cancer by Histologic Subtype.” *American Journal of Epidemiology* 171, no. 1 (January 1, 2010): 45–53.

Gates, Margaret A., Shelley S. Tworoger, Kathryn L. Terry, Linda Titus-Ernstoff, Bernard Rosner, Immaculata De Vivo, Daniel W. Cramer, and Susan E. Hankinson. “Talc Use, Variants of the GSTM1, GSTT1, and NAT2 Genes, and Risk of Epithelial Ovarian Cancer.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 17, no. 9 (September 2008): 2436–44.

Genofre, Eduardo H., Francisco S. Vargas, Milena M. P. Acencio, Leila Antonangelo, Lisete R. Teixeira, and Evaldo Marchi. “Talc Pleurodesis: Evidence of Systemic Inflammatory Response to Small Size Talc Particles.” *Respiratory Medicine* 103, no. 1 (January 2009): 91–97.

Germani, D., S. Belli, C. Bruno, M. Grignoli, M. Nesti, R. Pirastu, and P. Comba. “Cohort Mortality Study of Women Compensated for Asbestosis in Italy.” *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 129–34.

Gertig, D. M., D. J. Hunter, D. W. Cramer, G. A. Colditz, F. E. Speizer, W. C. Willett, and S. E. Hankinson. “Prospective Study of Talc Use and Ovarian Cancer.” *Journal of the National Cancer Institute* 92, no. 3 (February 2, 2000): 249–52.

Ghio, Andrew J., Joleen M. Soukup, Lisa A. Dailey, Judy H. Richards, Jennifer L. Turi, Elizabeth N. Pavlisko, and Victor L. Roggli. “Disruption of Iron Homeostasis in Mesothelial Cells after Talc Pleurodesis.” *American Journal of Respiratory Cell and Molecular Biology* 46, no. 1 (January 1, 2012): 80–86.

Gibbs, A.E., F.D. Pooley, M. Griffiths, R. Mitha, J.E. Craighead, J.R. Ruttner. “Talc Pneumoconiosis: A Pathologic and Mineralogic Study.” *Human Pathology* 23, No. 12, (December 1992): 1344-1354.

Gloyne, S. R. “Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis.”

Tubercle 17 (1935): 5–10.
Godard, B., W. D. Foulkes, D. Provencher, J. S. Brunet, P. N. Tonin, A. M. Mes-Masson, S. A. Narod, and P. Ghadirian. "Risk Factors for Familial and Sporadic Ovarian Cancer among French Canadians: A Case-Control Study." *American Journal of Obstetrics and Gynecology* 179, no. 2 (August 1998): 403–10.
Gondal, M., et al. "Detection of Tox Metals (Lead and Chromium) in Talcum Powder Using Laser Induced Breakdown Spectroscopy." *Applied Optics* 51, No. 30, (October 2012): 7395-7401.
Gonzalez, Kelly D., Katie A. Noltner, Carolyn H. Buzin, Dongqing Gu, Cindy Y. Wen-Fong, Vu Q. Nguyen, Jennifer H. Han, et al. "Beyond Li Fraumeni Syndrome: Clinical Characteristics of Families with P53 Germline Mutations." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 27, no. 8 (March 10, 2009): 1250–56.
Gonzalez, Nicole L., Katie M. O'Brien, Aimee A. D'Aloisio, Dale P. Sandler, and Clarice R. Weinberg. "Douching, Talc Use, and Risk of Ovarian Cancer." *Epidemiology (Cambridge, Mass.)* 27, no. 6 (2016): 797–802.
Goodman, Marc T, Galina Lurie, Pamela J Thompson, Katharine E McDuffie, and Michael E Carney. "Association of Two Common Single-Nucleotide Polymorphisms in the CYP19A1 Locus and Ovarian Cancer Risk." *Endocrine-Related Cancer* 15, no. 4 (December 2008): 1055–60.
Gordon, Ronald E., Sean Fitzgerald, and James Millette. "Asbestos in Commercial Cosmetic Talcum Powder as a Cause of Mesothelioma in Women." *International Journal of Occupational and Environmental Health* 20, no. 4 (October 2014): 318–32.
Graham, J., and R. Graham. "Ovarian Cancer and Asbestos." *Environmental Research* 1, no. 2 (October 1967): 115–28.
Graham, and Jenkins. "Value of Modified Starch as a Substitute for Talc." *Lancet (London, England)* 1, no. 6708 (March 22, 1952): 590–91.
Green, A., D. Purdie, C. Bain, V. Siskind, P. Russell, M. Quinn, and B. Ward. "Tubal Sterilisation, Hysterectomy and Decreased Risk of Ovarian Cancer. Survey of Women's Health Study Group." *International Journal of Cancer. Journal International Du Cancer* 71, no. 6 (June 11, 1997): 948–51.
Grivennikov, Sergei I., Florian R. Greten, and Michael Karin. "Immunity, Inflammation, and Cancer." *Cell* 140, no. 6 (March 19, 2010): 883–99.
Gross, A. J., and P. H. Berg. "A Meta-Analytical Approach Examining the Potential Relationship between Talc Exposure and Ovarian Cancer." *Journal of Exposure Analysis and Environmental Epidemiology* 5, no. 2 (June 1995): 181–95.
Hall, J. M., M. K. Lee, B. Newman, J. E. Morrow, L. A. Anderson, B. Huey, and M. C. King. "Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21." *Science (New York, N.Y.)* 250, no. 4988 (December 21, 1990): 1684–89.
Halme, J., M. G. Hammond, J. F. Hulka, S. G. Raj, and L. M. Talbert. "Retrograde Menstruation in Healthy Women and in Patients with Endometriosis." *Obstetrics and Gynecology* 64, no. 2 (August 1984): 151–54.
Hamilton, T. C., H. Fox, C. H. Buckley, W. J. Henderson, and K. Griffiths. "Effects of Talc on the Rat Ovary." *British Journal of Experimental Pathology* 65, no. 1 (February 1984): 101–6.
Hanahan, Douglas and Robert A. Weinberg. "Hallmarks of Cancer: The Next Generation." *Cell*

144, (March 4, 2011): 646-674.
Hankinson, S. E., D. J. Hunter, G. A. Colditz, W. C. Willett, M. J. Stampfer, B. Rosner, C. H. Hennekens, and F. E. Speizer. “Tubal Ligation, Hysterectomy, and Risk of Ovarian Cancer. A Prospective Study.” *JAMA* 270, no. 23 (December 15, 1993): 2813–18.
Hannenhalli, Sridhar, and Klaus H. Kaestner. “The Evolution of Fox Genes and Their Role in Development and Disease.” *Nature Reviews. Genetics* 10, no. 4 (April 2009): 233–40.
Harlow, B. L., D. W. Cramer, D. A. Bell, and W. R. Welch. “Perineal Exposure to Talc and Ovarian Cancer Risk.” *Obstetrics and Gynecology* 80, no. 1 (July 1992): 19–26.
Harlow, B. L., and P. A. Hartge. “A Review of Perineal Talc Exposure and Risk of Ovarian Cancer.” *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 254–60.
Harlow, B. L., and N. S. Weiss. “A Case-Control Study of Borderline Ovarian Tumors: The Influence of Perineal Exposure to Talc.” *American Journal of Epidemiology* 130, no. 2 (August 1989): 390–94.
Harper, Amy K, and Ghassan Saed. “"Talc Induces a pro-Oxidant State in Normal and Ovarian Cancer Cells through Genetic Point Mutations in Key Redox Enzymes,” Accepted for Presentation at SGO Meeting,” In Press 2019.
Hartge, P., R. Hoover, L. P. Lesher, and L. McGowan. “Talc and Ovarian Cancer.” *JAMA: The Journal of the American Medical Association* 250, no. 14 (October 14, 1983): 1844.
Hasselbalch, Hans Carl. “Chronic Inflammation as a Promotor of Mutagenesis in Essential Thrombocythemia, Polycythemia Vera and Myelofibrosis. A Human Inflammation Model for Cancer Development?” *Leukemia Research* 37, no. 2 (February 2013): 214–20.
Havrilesky, Laura J., Patricia G. Moorman, William J. Lowery, Jennifer M. Gierisch, Remy R. Coeytaux, Rachel Peragallo Urrutia, Michaela Dinan, et al. “Oral Contraceptive Pills as Primary Prevention for Ovarian Cancer: A Systematic Review and Meta-Analysis.” *Obstetrics and Gynecology* 122, no. 1 (July 2013): 139–47.
Heller, D. S., R. E. Gordon, and N. Katz. “Correlation of Asbestos Fiber Burdens in Fallopian Tubes and Ovarian Tissue.” *American Journal of Obstetrics and Gynecology* 181, no. 2 (August 1999): 346–47.
Heller, D. S., R. E. Gordon, C. Westhoff, and S. Gerber. “Asbestos Exposure and Ovarian Fiber Burden.” *American Journal of Industrial Medicine* 29, no. 5 (May 1996): 435–39.
Heller, D. S., C. Westhoff, R. E. Gordon, and N. Katz. “The Relationship between Perineal Cosmetic Talc Usage and Ovarian Talc Particle Burden.” *American Journal of Obstetrics and Gynecology* 174, no. 5 (May 1996): 1507–10.
Henderson, W. J., T. C. Hamilton, M. S. Baylis, C. G. Pierrepoint, and K. Griffiths. “The Demonstration of the Migration of Talc from the Vagina and Posterior Uterus to the Ovary in the Rat.” *Environmental Research* 40, no. 2 (August 1986): 247–50.
Henderson, W. J., T. C. Hamilton, and K. Griffiths. “Talc in Normal and Malignant Ovarian Tissue.” *The Lancet* (March 3, 1979): 499.
Henderson, W. J., C. A. Joslin, A. C. Turnbull, and K. Griffiths. “Talc and Carcinoma of the Ovary and Cervix.” *The Journal of Obstetrics and Gynaecology of the British Commonwealth* 78, no. 3 (March 1971): 266–72.
Hernán, Miguel A. “The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data.” *American Journal of Public Health* 108, no. 5 (May 2018): 616–19.
Hill, Austin Bradford. “The Environment and Disease: Association or Causation?” *Proceedings*

of the Royal Society of Medicine 58, no. 5 (May 1965): 295–300.
Hillegass, Jedd M., Arti Shukla, Maximilian B. MacPherson, Jeffrey P. Bond, Chad Steele, and Brooke T. Mossman. "Utilization of Gene Profiling and Proteomics to Determine Mineral Pathogenicity in a Human Mesothelial Cell Line (LP9/TERT-1)." *Journal of Toxicology and Environmental Health. Part A* 73, no. 5 (January 2010): 423–36.
Hollinger, Mannfred. "Pulmonary Toxicity of Inhaled and Intravenous Talc." *Toxicology Letters* 52 (1990): 121-127.
Horowitz, Neil S., Austin Miller, Bunja Rungruang, Scott D. Richard, Noah Rodriguez, Michael A. Bookman, Chad A. Hamilton, Thomas C. Krivak, and G. Larry Maxwell. "Does Aggressive Surgery Improve Outcomes? Interaction between Preoperative Disease Burden and Complex Surgery in Patients with Advanced-Stage Ovarian Cancer: An Analysis of GOG 182." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 33, no. 8 (March 10, 2015): 937–43.
Houghton, Serena C., Katherine W. Reeves, Susan E. Hankinson, Lori Crawford, Dorothy Lane, Jean Wactawski-Wende, Cynthia A. Thomson, Judith K. Ockene, and Susan R. Sturgeon. "Perineal Powder Use and Risk of Ovarian Cancer." *Journal of the National Cancer Institute* 106, no. 9 (September 2014).
Huncharek, Michael, J. F. Geschwind, and Bruce Kupelnick. "Perineal Application of Cosmetic Talc and Risk of Invasive Epithelial Ovarian Cancer: A Meta-Analysis of 11,933 Subjects from Sixteen Observational Studies." *Anticancer Research* 23, no. 2C (April 2003): 1955–60.
Huncharek, Michael, Joshua Muscat, Adedayo Onitilo, and Bruce Kupelnick. "Use of Cosmetic Talc on Contraceptive Diaphragms and Risk of Ovarian Cancer: A Meta-Analysis of Nine Observational Studies." *European Journal of Cancer Prevention: The Official Journal of the European Cancer Prevention Organisation (ECP)* 16, no. 5 (October 2007): 422–29.
Hunn, Jessica, and Gustavo C. Rodriguez. "Ovarian Cancer: Etiology, Risk Factors, and Epidemiology." *Clinical Obstetrics and Gynecology* 55, no. 1 (March 2012): 3–23.
IARC. "Mechanisms of Fibre Carcinogens." *IARC Scientific Publications.* No. 140. 1996.
IARC. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans – IARC: Asbestos," 1977.
IARC. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 58. Beryllium, Cadmium, Mercury, and Exposures in the Glass Manufacturing Industry," 1993.
IARC. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 93 Carbon Black, Titanium Dioxide, and Talc." *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans / World Health Organization, International Agency for Research on Cancer* 93 (2010): 1–413.
IARC. "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100C," 2012.
IARC. "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica and Some Silicates." IARC, 1987.
IARC. "IARC Monographs on the Evaluation of the Carcinogenic Risks to Humans. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1-42. Supplement 7," 1987.
IARC, International Agency for Research on Cancer, and World Health Organization, eds.

Carbon Black, Titanium Dioxide, and Talc. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, v. 93. Lyon, France: Geneva: International Agency for Research on Cancer; Distributed by WHO Press, 2010.

"Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer." *Cell Cycle* 8, no. 19 (2009): 3107–11.

Institute of Medicine (US) Committee on Asbestos: Selected Health Effects. *Asbestos: Selected Cancers*. The National Academies Collection: Reports Funded by National Institutes of Health. Washington (DC): National Academies Press (US), 2006.

Isaacs, Claudine, and Beth N Peshkin. "Management of Patients at High Risk for Breast and Ovarian Cancer." *UpToDate*, 2018.

Iturralde, M., and P. F. Venter. "Hysterosalpingo-Radionuclide Scintigraphy (HERS)." *Seminars in Nuclear Medicine* 11, no. 4 (October 1981): 301–14.

J. Lightfoot, G.A. Kingston, and F.D. Pooley. "An Examination of Italian Mine Samples and Relevant Powders," 1972.

Jaiswal, M., N. F. LaRusso, L. J. Burgart, and G. J. Gores. "Inflammatory Cytokines Induce DNA Damage and Inhibit DNA Repair in Cholangiocarcinoma Cells by a Nitric Oxide-Dependent Mechanism." *Cancer Research* 60, no. 1 (January 1, 2000): 184–90.

"JANSSEN-000056 P-23 (Pltf_MISC_00000321) Ortho Diaphragm Information," n.d.

Jasuja, S. et al. "Cosmetic Talc-Related Pulmonary Granulomatosis." *Journal of Investigative Medicine High Impact Case Reports* (July-September 2017): 1–4.

Jaurand, M. C. "Mechanisms of Fiber-Induced Genotoxicity." *Environmental Health Perspectives* 105 Suppl 5 (September 1997): 1073–84.

Jaurand, M. C. "Particulate-State Carcinogenesis: A Survey of Recent Studies on the Mechanisms of Action of Fibres." *IARC Scientific Publications*, no. 90 (1989): 54–73.

Jaurand, MC. "Mechanisms of Fibre Genotoxicity." In *Mechanisms in Fibre Carcinogensis*. New York: Plenum Press, 1991.

Jervis, Sarah, Honglin Song, Andrew Lee, Ed Dicks, Jonathan Tyrer, Patricia Harrington, Douglas F. Easton, Ian J. Jacobs, Paul P. D. Pharoah, and Antonis C. Antoniou. "Ovarian Cancer Familial Relative Risks by Tumour Subtypes and by Known Ovarian Cancer Genetic Susceptibility Variants." *Journal of Medical Genetics* 51, no. 2 (February 2014): 108–13.

Jia, D, Y Nagaoka, S Orsulic, and M Katsumata. "Inflammation Is a Key Contributor to Ovarian Cancer Cell Seeding." *Scientific Reports* 8, no. 12394 (August 17, 2018).

Jiang, Zhongliang, Nicole M. Fletcher, Rouba Ali-Fehmi, Michael P. Diamond, Husam M. Abu-Soud, Adnan R. Munkarah, and Ghassan M. Saed. "Modulation of Redox Signaling Promotes Apoptosis in Epithelial Ovarian Cancer Cells." *Gynecologic Oncology* 122, no. 2 (August 2011): 418–23.

John M. DeSesso. "Exponent Talc Defense Presentation Toxic Talc?" January 18, 2018.

Jones, Richard E., and Kristin H. Lopez. "Human Reproductive Biology - 4th Edition Chapter 9 - Gamete Transport and Fertilization." In *Human Reproductive Biology*, Third., 159–73. San Diego: Academic Press, 2006.

Jordan, SJ, KL Cushing-Haugen, KG Wicklund, JA Doherty, and MA Rossing. "Breast Feeding and Risk of Epithelial Ovarian Cancer." *Cancer Causes & Control: CCC* 23, no. 6 (June 2012): 919–27.

Jordan, Susan J., Victor Siskind, Adèle C Green, David C. Whiteman, and Penelope M. Webb. "Breastfeeding and Risk of Epithelial Ovarian Cancer." *Cancer Causes & Control: CCC*

21, no. 1 (January 2010): 109–16.

Jordan, Susan J., David C. Whiteman, David M. Purdie, Adèle C. Green, and Penelope M. Webb. "Does Smoking Increase Risk of Ovarian Cancer? A Systematic Review." *Gynecologic Oncology* 103, no. 3 (December 2006): 1122–29.

Jurinski, Joseph B., and J. Donald Rimstidt. "Biodurability of Talc." *American Mineralogist* 86, no. 4 (April 2001): 392–99.

Kane, AB, P Boffetta, R Saracci, and JD Wilbourn. "Mechanisms of Fibre Carcinogenesis." IARC, 1996.

Kang, N., D. Griffin, and H. Ellis. "The Pathological Effects of Glove and Condom Dusting Powders." *Journal of Applied Toxicology* 12, no. 6 (December 1992): 443–49.

Kanterman, J., Moshe Sade-Feldman, Michal Baniyash. "New Insights into Chronic Inflammation-Induced Immunosuppression." *Seminars in Cancer Biology* 22 (2012): 307– 318.

Karageorgi, Stalo, Margaret A. Gates, Susan E. Hankinson, and Immaculata De Vivo. "Perineal Use of Talcum Powder and Endometrial Cancer Risk." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 19, no. 5 (May 2010): 1269–75.

Kasper, C. S., and P. J. Chandler. "Possible Morbidity in Women from Talc on Condoms." *JAMA: The Journal of the American Medical Association* 273, no. 11 (March 15, 1995): 846–47.

Kauff, Noah D., Nandita Mitra, Mark E. Robson, Karen E. Hurley, Shaokun Chuai, Deborah Goldfrank, Eve Wadsworth, et al. "Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation-Negative Hereditary Breast Cancer Families." *Journal of the National Cancer Institute* 97, no. 18 (September 21, 2005): 1382–84.

Keal, E.E. "Asbestosis and Abdominal Neoplasms." *The Lancet* (December 3, 1960): 1211-1260.

Keskin, Nadi, Yasemin Aktan Teksen, Esra Gürlek Ongun, Yusuf Ozay, and Halil Saygili. "Does Long-Term Talc Exposure Have a Carcinogenic Effect on the Female Genital System of Rats? An Experimental Pilot Study." *Archives of Gynecology and Obstetrics* 280, no. 6 (December 2009): 925–31.

Khan, Mohd Imran, AmoghA. Sahasrabuddhe, Govil Patil, Mohd Javed Akhtar, Mohd Ashquin, and Iqbal Ahmad. "Nano-Talc Stabilizes TNF- α m-RNA in Human Macrophages." *Journal of Biomedical Nanotechnology* 7, no. 1 (January 1, 2011): 112–13.

King, HM. "Talc: The Softest Mineral.,"

King, Talmadge. "Asbestos-Related Pleuropulmonary Disease." Edited by Kevin Flaherty. *UpToDate*, 2018.

Kiraly, Orsolya, Guanyu Gong, Werner Olipitz, Sureshkumar Muthupalani, and Bevin P. Engelward. "Inflammation-Induced Cell Proliferation Potentiates DNA Damage-Induced Mutations In Vivo." *PLoS Genetics*, February 3, 2015.

Kissler, Stefan, Ernst Siebzehnruebl, Joachim Kohl, Anja Mueller, Nadja Hamscho, Regine Gaetje, Andre Ahr, Achim Rody, and Manfred Kaufmann. "Uterine Contractility and Directed Sperm Transport Assessed by Hysterosalpingoscintigraphy (HSSG) and Intrauterine Pressure (IUP) Measurement." *Acta Obstetricia Et Gynecologica Scandinavica* 83, no. 4 (April 2004): 369–74.

Klampfer, Lidija. "Cytokines, Inflammation and Colon Cancer." *Current Cancer Drug Targets*

11, no. 4 (May 2011): 451–64.
Knudson, A. G. “Mutation and Cancer: Statistical Study of Retinoblastoma.” *Proceedings of the National Academy of Sciences of the United States of America* 68, no. 4 (April 1971): 820–23.
Kunz, G., D. Beil, H. Deiniger, A. Einspanier, G. Mall, and G. Leyendecker. “The Uterine Peristaltic Pump. Normal and Impeded Sperm Transport within the Female Genital Tract.” *Advances in Experimental Medicine and Biology* 424 (1997): 267–77.
Kurman, Robert J., and Ie-Ming Shih. “Molecular Pathogenesis and Extraovarian Origin of Epithelial Ovarian Cancer. Shifting the Paradigm.” *Human Pathology* 42, no. 7 (July 2011): 918–31.
Kurman, Robert J. “The Dualistic Model of Ovarian Carcinogenesis.” *The American Journal of Pathology* 186, no. 4 (April 1, 2016): 733–47.
Kurman, Robert J., “The Origin and Pathogenesis of Epithelial Ovarian Cancer: A Proposed Unifying Theory.” *The American Journal of Surgical Pathology* 34, no. 3 (March 2010): 433–43.
Kurta, Michelle L., Kirsten B. Moysich, Joel L. Weissfeld, Ada O. Youk, Clareann H. Bunker, Robert P. Edwards, Francesmary Modugno, Roberta B. Ness, and Brenda Diergaarde. “Use of Fertility Drugs and Risk of Ovarian Cancer: Results from a US-Based Case-Control Study.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 21, no. 8 (August 2012): 1282–92.
La Vecchia. “Ovarian Cancer: Epidemiology and Risk Factors.” *European Journal of Cancer Prevention* 26 (2017): 55–62.
Lambert, C., et al. “A Case-Control Study of Mesothelioma in Minnesota Iron Ore (Taconite) Miners.” *Occup Environ Med* 73 (2016):103–109.
Lancaster, Johnathan M., C. Bethan Powell, Lee-may Chen, and Debra L. Richardson. “Society of Gynecologic Oncology Statement on Risk Assessment for Inherited Gynecologic Cancer Predispositions.” *Gynecologic Oncology* 136, no. 1 (January 2015): 3–7.
Landen, Charles N., Michael J. Birrer, and Anil K. Sood. “Early Events in the Pathogenesis of Epithelial Ovarian Cancer.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 26, no. 6 (February 20, 2008): 995–1005.
Langseth, H., S. E. Hankinson, J. Siemiatycki, and E. Weiderpass. “Perineal Use of Talc and Risk of Ovarian Cancer.” *Journal of Epidemiology and Community Health* 62, no. 4 (April 2008): 358–60.
Langseth, H., B.V. Johansen, J.M. Nesland, and K. Kjaerheim. “Asbestos Fibers in Ovarian Tissue from Norwegian Pulp and Paper Workers.” *International Journal of Gynecological Cancer* 17, no. 1 (January 2007): 44–49.
Langseth, Hilde, and Kristina Kjaerheim. “Ovarian Cancer and Occupational Exposure among Pulp and Paper Employees in Norway.” *Scandinavian Journal of Work, Environment & Health* 30, no. 5 (October 2004): 356–61.
Lanphear, B. P., and C. R. Buncher. “Latent Period for Malignant Mesothelioma of Occupational Origin.” *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 34, no. 7 (July 1992): 718–21.
Lee, Jennifer S., Esther M. John, Valerie McGuire, Anna Felberg, Kimberly L. Ostrow, Richard A. DiCioccio, Frederick P. Li, Alexander Miron, Dee W. West, and Alice S. Whittemore. “Breast and Ovarian Cancer in Relatives of Cancer Patients, with and without BRCA

Mutations." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 15, no. 2 (February 2006): 359–63.

Leikauf, George. "Toxic Responses of the Respiratory System." Chapter 15. 2013.

Levanon, Keren, Christopher Crum, and Ronny Drapkin. "New Insights into the Pathogenesis of Serous Ovarian Cancer and Its Clinical Impact." *Journal of Clinical Oncology* 26, no. 32 (November 10, 2008): 5284–93

Levy-Lahad, E., and E. Friedman. "Cancer Risks among BRCA1 and BRCA2 Mutation Carriers." *British Journal of Cancer* 96, no. 1 (January 15, 2007): 11–15.

Levy, Stuart. "Pulmonary Reactions to Other Occupational Dusts and Fumes." *Occupational Medicine*. 3rd Edition. Mosby. 1994.

Lin, Hui-Wen, Ying-Yueh Tu, Shiyng Yu Lin, Wei-Ju Su, Wei Li Lin, Wei Zer Lin, Shen-Chi Wu, and Yuen-Liang Lai. "Risk of Ovarian Cancer in Women with Pelvic Inflammatory Disease: A Population-Based Study." *The Lancet. Oncology* 12, no. 9 (September 2011): 900–904.

Liou, Geou-Yarh, and Peter Storz. "Reactive Oxygen Species in Cancer." *Free Radical Research* 44, no. 5 (May 2010): 476–96.

Liu, D. T., and A. Hitchcock. "Endometriosis: Its Association with Retrograde Menstruation, Dysmenorrhoea and Tubal Pathology." *British Journal of Obstetrics and Gynaecology* 93, no. 8 (August 1986): 859–62.

Lo-Ciganic, Wei-Hsuan, Janice C. Zgibor, Clareann H. Bunker, Kirsten B. Moysich, Robert P. Edwards, and Roberta B. Ness. "Aspirin, Nonaspirin Nonsteroidal Anti-Inflammatory Drugs, or Acetaminophen and Risk of Ovarian Cancer." *Epidemiology (Cambridge, Mass.)* 23, no. 2 (March 2012): 311–19.

Lockey, J. E. "Nonasbestos Fibrous Minerals." *Clinics in Chest Medicine* 2, no. 2 (May 1981): 203–18.

Longo, D. L., and R. C. Young. "Cosmetic Talc and Ovarian Cancer." *Lancet* 2, no. 8138 (August 18, 1979): 349–51.

Luan, Nan-Nan, Qi-Jun Wu, Ting-Ting Gong, Emily Vogtmann, Yong-Lai Wang, and Bei Lin. "Breastfeeding and Ovarian Cancer Risk: A Meta-Analysis of Epidemiologic Studies1234." *The American Journal of Clinical Nutrition* 98, no. 4 (October 2013): 1020–31.

Lundin, Eva, Laure Dossus, Tess Clendenen, Vittorio Krogh, Kjell Grankvist, Marianne Wulff, Sabina Sieri, et al. "C-Reactive Protein and Ovarian Cancer: A Prospective Study Nested in Three Cohorts (Sweden, USA, Italy)." *Cancer Causes & Control: CCC* 20, no. 7 (September 2009): 1151–59.

Madsen, Cecilie, Louise Baandrup, Christian Dehlendorff, and Susanne K. Kjaer. "Tubal Ligation and Salpingectomy and the Risk of Epithelial Ovarian Cancer and Borderline Ovarian Tumors: A Nationwide Case-Control Study." *Acta Obstetricia Et Gynecologica Scandinavica* 94, no. 1 (January 2015): 86–94.

Magnani, C., D. Ferrante, F. Barone-Adesi, M. Bertolotti, A. Todesco, D. Mirabelli, and B. Terracini. "Cancer Risk after Cessation of Asbestos Exposure: A Cohort Study of Italian Asbestos Cement Workers." *Occupational and Environmental Medicine* 65, no. 3 (March 2008): 164–70.

Mäki-Nevala, Satu, Virinder Kaur Sarhadi, Aija Knuuttila, Ilari Scheinin, Pekka Ellonen, Sonja Lagström, Mikko Rönty, et al. "Driver Gene and Novel Mutations in Asbestos-Exposed

Lung Adenocarcinoma and Malignant Mesothelioma Detected by Exome Sequencing." *Lung* 194, no. 1 (February 2016): 125–35.
Mallen, Adrianne R., Mary K. Townsend, and Shelley S. Tworoger. "Risk Factors for Ovarian Carcinoma." *Hematology/Oncology Clinics of North America*, September 2018.
Mandel, J., et al. "A Review of Mortality Associated with Elongate Mineral Particle (EMP) Exposure in Occupational Epidemiology Studies of Gold, Talc, and Taconite Mining." *American Journal of Industrial Medicine* 59 (2016): 1047-1060.
Mannino, David M. "Cigarette Smoking and Other Possible Risk Factors for Lung Cancer." *UpToDate*, 2018.
Mattenklott, M. "Asbestos in Talc Powders and Soapstone – The Present State." *Gefahrstoffe-Reinhalt.* Luft 67 No. 7/8 (2007): 287-291.
McCullough, Marie. "Condom Makers Stop Using Talc." *Asbury Park Press*. January 16, 1996.
McCullough, Marie. "Women's Health Concerns Prompt Condom Makers to Stop Using Talc." *Jersey Journal*. April 17, 1996, City Edition.
McLaughlin-Drubin, Margaret E., and Karl Munger. "Viruses Associated with Human Cancer." *Biochimica et Biophysica Acta* 1782, no. 3 (March 2008): 127–50.
McLemore, Miaskowski, Chen Aouizerat, and Dodd. "Epidemiological and Genetic Factors Associated With Ovarian Cancer." *Cancer Nursing* 32, no. 4 (2009): 281–88.
Melaiu, Ombretta, Federica Gemignani, and Stefano Landi. "The Genetic Susceptibility in the Development of Malignant Pleural Mesothelioma." *Journal of Thoracic Disease* 10, no. Suppl 2 (January 2018): S246–52.
Meng, Qingsong, Weixue Sun, John Jiang, Nicole M. Fletcher, Michael P. Diamond, and Ghassan M. Saed. "Identification of Common Mechanisms between Endometriosis and Ovarian Cancer." *Journal of Assisted Reproduction and Genetics* 28 (2011): 917–23.
Merritt, Melissa A., Adèle C. Green, Christina M. Nagle, Penelope M. Webb, Australian Cancer Study (Ovarian Cancer), and Australian Ovarian Cancer Study Group. "Talcum Powder, Chronic Pelvic Inflammation and NSAIDs in Relation to Risk of Epithelial Ovarian Cancer." *International Journal of Cancer. Journal International Du Cancer* 122, no. 1 (January 1, 2008): 170–76.
Miller, Diane M, and Jessica N. McAlpine. "Opportunistic Salpingectomy for Ovarian, Fallopian Tubal, and Peritoneal Carcinoma Risk Reduction." *UpToDate*, 2018.
Mills, Paul K., Deborah G. Riordan, Rosemary D. Cress, and Heather A. Young. "Perineal Talc Exposure and Epithelial Ovarian Cancer Risk in the Central Valley of California." *International Journal of Cancer. Journal International Du Cancer* 112, no. 3 (November 10, 2004): 458–64.
Milne, R. L., and A. C. Antoniou. "Genetic Modifiers of Cancer Risk for BRCA1 and BRCA2 Mutation Carriers." *Annals of Oncology: Official Journal of the European Society for Medical Oncology* 22 Suppl 1 (January 2011): i11-17.
Milne, Roger L., and Antonis C. Antoniou. "Modifiers of Breast and Ovarian Cancer Risks for BRCA1 and BRCA2 Mutation Carriers." *Endocrine-Related Cancer* 23, no. 10 (2016): T69-84.
Moller, Danielsen, and Roursgaard Jantzen. "Oxidatively Damaged DNA in Animals Exposed to Particles." *Critical Reviews in Toxicology* 43, no. 2 (2013): 96–118.
Moon, Min Chaul, Jung Duck Park, Byung Soon Choi, So Young Park, Dong Won Kim, Yong Hyun Chung, Naomi Hisanaga, and Il Je Yu. "Risk Assessment of Baby Powder Exposure through Inhalation." *Toxicological Research* 27, no. 3 (September 2011):

137–41.
Moorman, Patricia G. “Scientific Review of the Epidemiologic Evidence on Talc Use and Ovarian Cancer,” February 2018.
Moorman, Patricia G., Rachel T. Palmieri, Lucy Akushevich, Andrew Berchuck, and Joellen M. Schildkraut. “Ovarian Cancer Risk Factors in African-American and White Women.” *American Journal of Epidemiology* 170, no. 5 (September 1, 2009): 598–606.
Moskowitz, Robert. “Talc Pneumoconiosis: A Treated Case.” *Chest* 58, No.1 (July 1970): 37-41.
Mostafa, S. A., C. B. Bargeron, R. W. Flower, N. B. Rosenshein, T. H. Parmley, and J. D. Woodruff. “Foreign Body Granulomas in Normal Ovaries.” *Obstetrics and Gynecology* 66, no. 5 (November 1985): 701–2.
Murphy, Megan A., Britton Trabert, Hannah P. Yang, Yikyung Park, Louise A. Brinton, Patricia Hartge, Mark E. Sherman, Albert Hollenbeck, and Nicolas Wentzensen. “Non-Steroidal Anti-Inflammatory Drug Use and Ovarian Cancer Risk: Findings from the NIH-AARP Diet and Health Study and Systematic Review.” *Cancer Causes & Control: CCC* 23, no. 11 (November 2012): 1839–52.
Muscat, J. E., and M. S. Huncharek. “Causation and Disease: Biomedical Science in Toxic Tort Litigation.” *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 31, no. 12 (December 1989): 997–1002.
Nadler, Diana L., and Igor G. Zurbenko. “Estimating Cancer Latency Times Using a Weibull Model,” 2014, 8.
Nam, Key and Douglas R. Gracey. “Pulmonary Talcosis from Cosmetic Talcum Powder.” *JAMA* 221, No. 5 (1972): 492-493.
Narod, Steven A. “Talc and Ovarian Cancer.” *Gynecologic Oncology* 141, no. 3 (2016): 410–12.
National Cancer Institute, Surveillance, Epidemiology, and End Results Program. “Cancer Stat Facts: Ovarian Cancer,” 2018.
National Cancer Institute. “NCI Dictionary of Cancer Terms: Pleurodesis.”
“National Toxicology Program (NTP) Technical Report (NTP TR 421) on the Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F1 Mice.” National Institutes of Health, 1993.
Nelson, Heather H., and Karl T. Kelsey. “The Molecular Epidemiology of Asbestos and Tobacco in Lung Cancer.” *Oncogene* 21, no. 48 (October 21, 2002): 7284–88.
Ness, R. B., and C. Cottreau. “Possible Role of Ovarian Epithelial Inflammation in Ovarian Cancer.” *JNCI Journal of the National Cancer Institute* 91, no. 17 (September 1, 1999): 1459–67.
Ness, R. B., J. A. Grisso, C. Cottreau, J. Klapper, R. Vergona, J. E. Wheeler, M. Morgan, and J. J. Schlesselman. “Factors Related to Inflammation of the Ovarian Epithelium and Risk of Ovarian Cancer.” *Epidemiology (Cambridge, Mass.)* 11, no. 2 (March 2000): 111–17.
Ness, Roberta B., Daniel W. Cramer, Marc T. Goodman, Susanne Krûger Kjaer, Kathy Mallin, Berit Jul Mosgaard, David M. Purdie, Harvey A. Risch, Ronald Vergona, and Anna H. Wu. “Infertility, Fertility Drugs, and Ovarian Cancer: A Pooled Analysis of Case-Control Studies.” *American Journal of Epidemiology* 155, no. 3 (February 1, 2002): 217–24.
Neutra, Raymond Richard, Carl F. Cranor, and David Gee. “The Use and Misuse of Bradford Hill in U.S. Tort Law.” *Jurimetrics J.*, 2018, 127–62.
Newhouse, M. L., G. Berry, J. C. Wagner, and M. E. Turok. “A Study of the Mortality of Female Asbestos Workers.” *British Journal of Industrial Medicine* 29, no. 2 (April 1972): 134–41.

Nick, Alpa M., Robert L. Coleman, Pedro T. Ramirez, and Anil K. Sood. “A Framework for a Personalized Surgical Approach to Ovarian Cancer.” *Nature Reviews. Clinical Oncology* 12, no. 4 (April 2015): 239–45.

NIOSH. “Asbestos Fibers and Other Elongated Mineral Particles: State of the Science and Roadmap for Research (Revised Draft),” January 2009.

NIOSH. “Fiber Exposure during Use of Baby Powders, Report No. IWS-36-6.,” July 1972.

NIOSH. 2011 Current Intelligence Bulletin No. 62,” 2011.

NIOSH. “Pocket Guide to Chemical Hazards: Asbestos.” Publication No. 2005-149 (September 2007).

Norquist, Barbara M., Maria I. Harrell, Mark F. Brady, Tom Walsh, Ming K. Lee, Suleyman Gulsuner, Sarah S. Bernards, et al. “Inherited Mutations in Women With Ovarian Carcinoma.” *JAMA Oncology* 2, no. 4 (April 2016): 482–90.

NTP. “Report on Carcinogens: Asbestos.” 14th Edition. 2016.

NTP. “NTP Technical Report on the Toxicology and Carcinogenesis Studies of Benzophenone (CAS No. 119-61-9) In F344/N Rats and B6C3F1 Mice,” February 2006.

NTP. “NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(NonAsbestiform) in F344/N.Rats and B6C3Fl Mice (Inhalation Studies),” 1993.

Oberdörster, Günter, Eva Oberdörster, and Jan Oberdörster. “Nanotoxicology: An Emerging Discipline Evolving from Studies of Ultrafine Particles.” *Environmental Health Perspectives* 113, no. 7 (July 2005): 823–39. https://doi.org/10.1289/ehp.7339.

Okada, Futoshi. “Beyond Foreign-Body-Induced Carcinogenesis: Impact of Reactive Oxygen Species Derived from Inflammatory Cells in Tumorigenic Conversion and Tumor Progression.” *International Journal of Cancer* 121, no. 11 (December 1, 2007): 2364–72.

Paoletti, L., S. Caiazza, G. Donelli, and F. Pocchiari. “Evaluation by Electron Microscopy Techniques of Asbestos Contamination in Industrial, Cosmetic, and Pharmaceutical Talcs.” *Regulatory Toxicology and Pharmacology: RTP* 4, no. 3 (September 1984): 222–35.

Park, Hyo K., Joellen M. Schildkraut, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa Bondy, Sydnee Crankshaw, et al. “Benign Gynecologic Conditions Are Associated with Ovarian Cancer Risk in African-American Women: A Case–Control Study.” *Cancer Causes & Control*, September 29, 2018.

Parmar, M. K. B., J. A. Ledermann, N. Colombo, A. du Bois, J.-F. Delaloye, G. B. Kristensen, S. Wheeler, et al. “Paclitaxel plus Platinum-Based Chemotherapy versus Conventional Platinum-Based Chemotherapy in Women with Relapsed Ovarian Cancer: The ICON4/AGO-OVAR-2.2 Trial.” *Lancet (London, England)* 361, no. 9375 (June 21, 2003): 2099–2106.

Parmley, T. H., and J. D. Woodruff. “The Ovarian Mesothelioma.” *American Journal of Obstetrics and Gynecology* 120, no. 2 (September 15, 1974): 234–41.

Pathology of Asbestos-Associated Diseases, 2011.

Pearce, Celeste Leigh, Claire Templeman, Mary Anne Rossing, Alice Lee, Aimee M Near, Penelope M Webb, Christina M Nagle, et al. “Association between Endometriosis and Risk of Histological Subtypes of Ovarian Cancer: A Pooled Analysis of Case–Control Studies.” *The Lancet Oncology* 13, no. 4 (April 2012): 385–94. https://doi.org/10.1016/S1470-2045(11)70404-1.

Pejovic, Tanja, and Farr Nezhat. “Missing Link: Inflammation and Ovarian Cancer.” *The Lancet.*

Oncology 12, no. 9 (September 2011): 833–34.
Pelling, D., and J. G. Evans. “Long-Term Peritoneal Tissue Response in Rats to Mould-Release Agents and Lubricant Powder Used on Surgeons’ Gloves.” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 24, no. 5 (May 1986): 425–30.
Penninkilampi, Ross, and Guy D. Eslick. “Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis.” *Epidemiology (Cambridge, Mass.)* 29, no. 1 (January 2018): 41–49.
Peshkin, B., et al. “Genetic Counseling and Testing for Hereditary Breast and Ovarian Cancer - UpToDate,” 2018. https://www.uptodate.com/contents/genetic-counseling-and-testing-for-hereditary-breast-and-ovarian-cancer?search=Genetic%20counseling%20and%20testing%20for%20hereditary%20breast%20and%20ovarian%20cancer&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
Peshkin, B. “Overview of Hereditary Breast and Ovarian Cancer Syndromes - UpToDate,” 2018. https://www.uptodate.com/contents/overview-of-hereditary-breast-and-ovarian-cancer-syndromes?search=Overview%20of%20hereditary%20breast%20and%20ovarian%20cancer%20syndromes&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
Peshkin, B. “Prevalence of BRCA1 and BRCA2 Mutations and Associated Cancer Risks - UpToDate,” 2018. https://www.uptodate.com/contents/prevalence-of-brca1-and-brca2-mutations-and-associated-cancer-risks?search=prevalence-of-brca1-and-brca2-mu%E2%80%A6search_result%26selectedTitle%3D1~73%26usage_type%3Ddefault%26display_rank%3D1&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2.
Phillips, J. C., P. J. Young, K. Hardy, and S. D. Gangolli. “Studies on the Absorption and Disposition of 3H-Labelled Talc in the Rat, Mouse, Guinea-Pig and Rabbit.” *Food and Cosmetics Toxicology* 16, no. 2 (April 1978): 161–63.
Pira, E, C Pelucchi, L Buffoni, A Palmas, M Turbiglio, E Negri, P G Piolatto, and C La Vecchia. “Cancer Mortality in a Cohort of Asbestos Textile Workers.” *British Journal of Cancer* 92, no. 3 (February 2005): 580–86.
Pira, Enrico, Canzio Romano, Francesco S. Violante, Andrea Farioli, Giovanna Spatari, Carlo La Vecchia, and Paolo Boffetta. “Updated Mortality Study of a Cohort of Asbestos Textile Workers.” *Cancer Medicine* 5, no. 9 (2016): 2623–28.
Porro, F. W., and N. M. Levine. “Pathology of Talc Pneumoconiosis with Report of an Autopsy.” *Northern New York Medical Journal* 3 (April 1946): 23–25.
Pott, R., and K. H. Friedrichs. “Tumors in Rats Following i.p. Injection of Fiberform Dusts.” *Naturwissenschaften* 59 (n.d.): 318–24.
Prat, Jaime, and FIGO Committee on Gynecologic Oncology. “Abridged Republication of FIGO’s Staging Classification for Cancer of the Ovary, Fallopian Tube, and Peritoneum.” *Cancer* 121, no. 19 (October 1, 2015): 3452–54.
Pukkala, Eero, Jan Ivar Martinsen, Elsebeth Lynge, Holmfridur Kolbrun Gunnarsdottir, Pär Sparén, Laufey Tryggvadottir, Elisabete Weiderpass, and Kristina Kjaerheim. “Occupation and Cancer - Follow-up of 15 Million People in Five Nordic Countries.” *Acta Oncologica (Stockholm, Sweden)* 48, no. 5 (2009): 646–790.
Purdie, D., A. Green, C. Bain, V. Siskind, B. Ward, N. Hacker, M. Quinn, G. Wright, P. Russell,

and B. Susil. “Reproductive and Other Factors and Risk of Epithelial Ovarian Cancer: An Australian Case-Control Study. Survey of Women’s Health Study Group.” *International Journal of Cancer. Journal International Du Cancer* 62, no. 6 (September 15, 1995): 678–84.

Purdie, David M., Christopher J. Bain, Victor Siskind, Penelope M. Webb, and Adèle C. Green. “Ovulation and Risk of Epithelial Ovarian Cancer.” *International Journal of Cancer. Journal International Du Cancer* 104, no. 2 (March 20, 2003): 228–32.

Radic, I, I Vucak, J Milosevic, A Marusic, S Vukicevic, and M Marusic. “Immunosuppression Induced by Talc Granulomatosis in the Rat.” *Clinical and Experimental Immunology* 73, no. 2 (August 1988): 316–21.

Ramus, Susan J., Antonis C. Antoniou, Karoline B. Kuchenbaecker, Penny Soucy, Jonathan Beesley, Xiaoqing Chen, Lesley McGuffog, et al. “Ovarian Cancer Susceptibility Alleles and Risk of Ovarian Cancer in BRCA1 and BRCA2 Mutation Carriers.” *Human Mutation* 33, no. 4 (April 2012): 690–702.

Rasool, Nabila, Amanda Nickles Fader, Leigh Seamon, Nikki L. Neubauer, Fadi Abu Shahin, Heather A. Alexander, Kathleen Moore, et al. “Stage I, Grade 3 Endometrioid Adenocarcinoma of the Endometrium: An Analysis of Clinical Outcomes and Patterns of Recurrence.” *Gynecologic Oncology* 116, no. 1 (January 2010): 10–14.

Rayburn, Elizabeth R., Scharri J. Ezell, and Ruiwen Zhang. “Anti-Inflammatory Agents for Cancer Therapy.” *Molecular and Cellular Pharmacology* 1, no. 1 (2009): 29–43.

Rebbeck, Timothy R., Nandita Mitra, Fei Wan, Olga M. Sinilnikova, Sue Healey, Lesley McGuffog, Sylvie Mazoyer, et al. “Association of Type and Location of BRCA1 and BRCA2 Mutations with Risk of Breast and Ovarian Cancer.” *JAMA* 313, no. 13 (April 7, 2015): 1347–61.

“Reference Manual on Scientific Evidence” Third Edition (2011).

Rehman, Ghana, et al. “Determination of Toxic Heavy Metals in Different Brands of Talcum Powder.” *International Journal of Applied and Natural Sciences (IJANS);* Vol. 2, Issue 2; (May 2013): 45-52.

Reid, A., J. Heyworth, N. de Klerk, and A. W. Musk. “The Mortality of Women Exposed Environmentally and Domestically to Blue Asbestos at Wittenoom, Western Australia.” *Occupational and Environmental Medicine* 65, no. 11 (November 2008): 743–49.

Reid, A., N. de Klerk, and A. W. Musk. “Does Exposure to Asbestos Cause Ovarian Cancer? A Systematic Literature Review and Meta-Analysis.” *Cancer Epidemiology Biomarkers & Prevention* 20, no. 7 (July 1, 2011): 1287–95.

Reid, A., N. H. de Klerk, C. Magnani, D. Ferrante, G. Berry, A. W. Musk, and E. Merler. “Mesothelioma Risk after 40 Years since First Exposure to Asbestos: A Pooled Analysis.” *Thorax* 69, no. 9 (September 2014): 843–50.

Reid, Alison, Amanda Segal, Jane S. Heyworth, Nicholas H. de Klerk, and Arthur W. Musk. “Gynecologic and Breast Cancers in Women after Exposure to Blue Asbestos at Wittenoom.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 18, no. 1 (January 2009): 140–47.

Reid, Brett M., Jennifer B. Permuth, and Thomas A. Sellers. “Epidemiology of Ovarian Cancer: A Review.” *Cancer Biology & Medicine* 14, no. 1 (February 2017): 9–32.

Reinhold, Robert. “Panel Finds Danger to the Environment from Technology.” *New York Times*; (December 29, 1968).

Reuter, Simone, Subash C. Gupta, Madan M. Chaturvedi, and Bharat B. Aggarwal. "Oxidative Stress, Inflammation, and Cancer: How Are They Linked?" *Free Radical Biology and Medicine* 49, no. 11 (December 1, 2010): 1603–16.

Rice, Megan S., Susan E. Hankinson, and Shelley S. Tworoger. "Tubal Ligation, Hysterectomy, Unilateral Oophorectomy, and Risk of Ovarian Cancer in the Nurses' Health Studies." *Fertility and Sterility* 102, no. 1 (July 2014): 192-198.e3. https://doi.org/10.1016/j.fertnstert.2014.03.041.

Ring, Kari L., Christine Garcia, Martha H. Thomas, and Susan C. Modesitt. "Current and Future Role of Genetic Screening in Gynecologic Malignancies." *American Journal of Obstetrics and Gynecology* 217, no. 5 (2017): 512–21.

Riska, A., J. I. Martinsen, K. Kjaerheim, E. Lynge, P. Sparen, L. Tryggvadottir, E. Weiderpass, and E. Pukkala. "Occupation and Risk of Primary Fallopian Tube Carcinoma in Nordic Countries." *International Journal of Cancer* 131, no. 1 (July 1, 2012): 186–92. https://doi.org/10.1002/ijc.26337.

Roggli, Victor L., Robin T. Vollmer, Kelly J. Butnor, and Thomas A. Sporn. "Tremolite and Mesothelioma." *Annals of Occupational Hygiene* 46, no. 5 (July 1, 2002): 447–53.

Rohl, A. N. "Asbestos in Talc." *Environmental Health Perspectives* 9 (December 1974): 129–32.

Rohl, A. N., A. M. Langer, I. J. Selikoff, A. Tordini, R. Klimentidis, D. R. Bowes, and D. L. Skinner. "Consumer Talcums and Powders: Mineral and Chemical Characterization." *Journal of Toxicology and Environmental Health* 2, no. 2 (November 1976): 255–84.

Roodhouse Gloyne, S. "Two Cases of Squamous Carcinoma of the Lung Occurring in Asbestosis." *Tubercle* 17, no. 1 (October 1935): 5-IN2.

Rosalind A. Eeles, Christine D. Berg, and Jeffery S. Tobias. *Cancer Prevention and Screening: Concepts, Principles and Controversies*. 1st ed. Accessed August 21, 2018. Rosenblatt, K. A., M. Szklo, and N. B. Rosenshein. "Mineral Fiber Exposure and the Development of Ovarian Cancer." *Gynecologic Oncology* 45, no. 1 (April 1992): 20–25.

Rosenblatt, Karin A., Noel S. Weiss, Kara L. Cushing-Haugen, Kristine G. Wicklund, and Mary Anne Rossing. "Genital Powder Exposure and the Risk of Epithelial Ovarian Cancer." *Cancer Causes & Control: CCC* 22, no. 5 (May 2011): 737–42.

Rösler, J. A., H. J. Woitowitz, H. J. Lange, R. H. Woitowitz, K. Ulm, and K. Rödelsperger. "Mortality Rates in a Female Cohort Following Asbestos Exposure in Germany." *Journal of Occupational Medicine.: Official Publication of the Industrial Medical Association* 36, no. 8 (August 1994): 889–93.

Ross, M. "Geology, Asbestos, and Health." *Environmental Health Perspectives* 9 (December 1974): 123–24.

Rothman, Kenneth J., Sander Greenland, and Timothy L. Lash. *Modern Epidemiology*. Lippincott Williams & Wilkins, 2008.

Saed, Ghassan M., Rouba Ali-Fehmi, Zhong L. Jiang, Nicole M. Fletcher, Michael P. Diamond, Husam M. Abu-Soud, and Adnan R. Munkarah. "Myeloperoxidase Serves as a Redox Switch That Regulates Apoptosis in Epithelial Ovarian Cancer." *Gynecologic Oncology* 116, no. 2 (February 2010): 276–81. https://doi.org/10.1016/j.ygyno.2009.11.004.

Saed, Ghassan M., Michael P. Diamond, and Nicole M. Fletcher. "Updates of the Role of Oxidative Stress in the Pathogenesis of Ovarian Cancer." *Gynecologic Oncology* 145, no. 3 (June 2017): 595–602. https://doi.org/10.1016/j.ygyno.2017.02.033.

Saed, Ghassan M., Nicole M. Fletcher, Michael P. Diamond, Robert T. Morris, Nardhy Gomez-Lopez, and Ira Memaj. "Novel Expression of CD11b in Epithelial Ovarian

Cancer: Potential Therapeutic Target." *Gynecologic Oncology* 148, no. 3 (2018): 567–75.

Saed, Ghassan M., Robert T. Morris, and Nicole M. Fletcher. *New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress*, 2018.

Schelz, John P. "The Detection of Chrysotile Asbestos at Low Levels in Talc by Differential Thermal Analysis." *Thermochimica Acta*, 8 (1974) 197-204.

Schenken, Robert S. "Endometriosis: Pathogenesis, Clinical Features, and Diagnosis." *UpToDate*, 2018.

Schildkraut, Joellen M., Sarah E. Abbott, Anthony J. Alberg, Elisa V. Bandera, Jill S. Barnholtz-Sloan, Melissa L. Bondy, Michele L. Cote, et al. "Association between Body Powder Use and Ovarian Cancer: The African American Cancer Epidemiology Study (AACES)." *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 25, no. 10 (2016): 1411–17.

Seeler, Albert O., M.D. "Toxic Hazards, Talc Pneumoconiosis." *The New England Journal of Medicine;* Vol. 261, No. 21 (Nov. 19, 1959) 1084-1085.

"SEER Cancer Statistics Review, 1975-2015, National Cancer Institute, Bethesda, MD, Based on November 2017 SEER Data Submission, Posted to the SEER Web Site," April 2018.

Selikoff, Irving J., et al. "Asbestos Exposure and Neoplasia." *JAMA*, Vol. 188, No. 1 (April 6, 1964) 142-146.

Shan, Weiwei, and Jinsong Liu. "Inflammation: A Hidden Path to Breaking the Spell of Ovarian Cancer." *Cell Cycle* 8, no. 19 (2009): 3107–11.

Shukla, Arti, Maximilian B. MacPherson, Jedd Hillegass, Maria E. Ramos-Nino, Vlada Alexeeva, Pamela M. Vacek, Jeffrey P. Bond, Harvey I. Pass, Chad Steele, and Brooke T. Mossman. "Alterations in Gene Expression in Human Mesothelial Cells Correlate with Mineral Pathogenicity." *American Journal of Respiratory Cell and Molecular Biology* 41, no. 1 (July 2009): 114–23.

Shushan, A., O. Paltiel, J. Iscovich, U. Elchalal, T. Peretz, and J. G. Schenker. "Human Menopausal Gonadotropin and the Risk of Epithelial Ovarian Cancer." *Fertility and Sterility* 65, no. 1 (January 1996): 13–18.

Singh, Naveena, C. Blake Gilks, Lynn Hirschowitz, Sean Kehoe, Iain A. McNeish, Dianne Miller, Raj Naik, Nafisa Wilkinson, and W. Glenn McCluggage. "Primary Site Assignment in Tubo-Ovarian High-Grade Serous Carcinoma: Consensus Statement on Unifying Practice Worldwide." *Gynecologic Oncology* 141, no. 2 (2016): 195–98.

Sjösten, A. C. E., H. Ellis, and G. a. B. Edelstam. "Retrograde Migration of Glove Powder in the Human Female Genital Tract." *Human Reproduction* 19, no. 4 (April 1, 2004): 991–95.

Soini, Tuuli, Ritva Hurskainen, Seija Grénman, Johanna Mäenpää, Jorma Paavonen, and Eero Pukkala. "Cancer Risk in Women Using the Levonorgestrel-Releasing Intrauterine System in Finland." *Obstetrics and Gynecology* 124, no. 2 Pt 1 (August 2014): 292–99.

Soong, Thing Rinda, Brooke E. Howitt, Alexander Miron, Neil S. Horowitz, Frank Campbell, Colleen M. Feltmate, Michael G. Muto, et al. "Evidence for Lineage Continuity between Early Serous Proliferations (ESPs) in the Fallopian Tube and Disseminated High-Grade Serous Carcinomas." *The Journal of Pathology*, July 25, 2018.

Stanton, M. F., M. Layard, A. Tegeris, E. Miller, M. May, E. Morgan, and A. Smith. "Relation of Particle Dimension to Carcinogenicity in Amphibole Asbestoses and Other Fibrous Minerals." *Journal of the National Cancer Institute* 67, no. 5 (November 1981): 965–75.

Starman, Daniel H., Leslie A. Litzky, and Larry R. Kaiser. "Epidemiology of Malignant Pleural

Mesothelioma." *UpToDate*, 2018.

Steiling, W., J. F. Almeida, H. Assaf Vandecasteele, S. Gilpin, T. Kawamoto, L. O'Keeffe, G. Pappa, K. Rettinger, H. Rothe, and A. M. Bowden. "Principles for the Safety Evaluation of Cosmetic Powders." *Toxicology Letters*, August 17, 2018.

Steiling, W., M. Bascompta, P. Carthew, G. Catalano, N. Corea, A. D'Haese, P. Jackson, et al. "Principle Considerations for the Risk Assessment of Sprayed Consumer Products." *Toxicology Letters* 227, no. 1 (May 16, 2014): 41–49.

Stewart, Louise M., C. D'Arcy J. Holman, Patrick Aboagye-Sarfo, Judith C. Finn, David B. Preen, and Roger Hart. "In Vitro Fertilization, Endometriosis, Nulliparity and Ovarian Cancer Risk." *Gynecologic Oncology* 128, no. 2 (February 2013): 260–64.

Stewart, Louise M., Katrina Spilsbury, Susan Jordan, Colin Stewart, C. D'Arcy J. Holman, Aime Powell, Joanne Reekie, and Paul Cohen. "Risk of High-Grade Serous Ovarian Cancer Associated with Pelvic Inflammatory Disease, Parity and Breast Cancer." *Cancer Epidemiology* 55 (August 2018): 110–16.

Straif, Kurt. "Update of the Scientific Evidence on Asbestos and Cancer." presented at the International Conference on Environmental and Occupational Determinants of Cancer: Interventions for Primary Prevention, Asturias (Avilés, Gijón), Spain, March 17, 2011.

Suzui, Masumi, et al. "Multiwalled Carbon Nanotubes Intratracheally Instilled into the Rat Lung Induce Development of Pleural Malignant Mesothelioma and Lung Tumors." *Cancer Sci*, 107 (2016) 924-935.

"Talc." *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans* 42 (1987): 185–224.

Tarchi, M., D. Orsi, P. Comba, M. De Santis, R. Pirastu, G. Battista, and M. Valiani. "Cohort Mortality Study of Rock Salt Workers in Italy." *American Journal of Industrial Medicine* 25, no. 2 (February 1994): 251–56.

Terry, Kathryn L., Stalo Karageorgi, Yurii B. Shvetsov, Melissa A. Merritt, Galina Lurie, Pamela J. Thompson, Michael E. Carney, et al. "Genital Powder Use and Risk of Ovarian Cancer: A Pooled Analysis of 8,525 Cases and 9,859 Controls." *Cancer Prevention Research (Philadelphia, Pa.)* 6, no. 8 (August 2013): 811–21.

Tewari, Devansu, James J. Java, Ritu Salani, Deborah K. Armstrong, Maurie Markman, Thomas Herzog, Bradley J. Monk, and John K. Chan. "Long-Term Survival Advantage and Prognostic Factors Associated with Intraperitoneal Chemotherapy Treatment in Advanced Ovarian Cancer: A Gynecologic Oncology Group Study." *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 33, no. 13 (May 1, 2015): 1460–66.

Thai, T. H., F. Du, J. T. Tsan, Y. Jin, A. Phung, M. A. Spillman, H. F. Massa, et al. "Mutations in the BRCA1-Associated RING Domain (BARD1) Gene in Primary Breast, Ovarian and Uterine Cancers." *Human Molecular Genetics* 7, no. 2 (February 1998): 195–202.

Thomas, Charles A., and Major G. Seelig. Powder lubricated surgeon's rubber glove. United States US2621333A, filed June 27, 1947, and issued December 16, 1952.

Torre, Lindsey A., Britton Trabert, Carol E. DeSantis, Kimberly D. Miller, Goli Samimi, Carolyn D. Runowicz, Mia M. Gaudet, Ahmedin Jemal, and Rebecca L. Siegel. "Ovarian Cancer Statistics, 2018." *CA: A Cancer Journal for Clinicians* 68, no. 4 (July 2018): 284–96.

Trabert, Britton. "Body Powder and Ovarian Cancer Risk – What Is the Role of Recall Bias?" *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American*

Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 25, no. 10 (October 2016): 1369–70.

Trabert, Britton, Ligia Pinto, Patricia Hartge, Troy Kemp, Amanda Black, Mark E. Sherman, Louise A. Brinton, et al. "Pre-Diagnostic Serum Levels of Inflammation Markers and Risk of Ovarian Cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial." *Gynecologic Oncology* 135, no. 2 (November 2014): 297–304.

Trabert, Britton, Elizabeth M Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L Anderson, Theodore M Brasky, et al. "Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium." *JNCI: Journal of the National*

Trabert, Britton, Elizabeth M. Poole, Emily White, Kala Visvanathan, Hans-Olov Adami, Garnet L. Anderson, Theodore M. Brasky, et al. "Analgesic Use and Ovarian Cancer Risk: An Analysis in the Ovarian Cancer Cohort Consortium." *Journal of the National Cancer Institute* 111, no. 2 (2019).

Tsilidis, K K, N E Allen, T J Key, L Dossus, A Lukanova, K Bakken, E Lund, et al. "Oral Contraceptive Use and Reproductive Factors and Risk of Ovarian Cancer in the European Prospective Investigation into Cancer and Nutrition." *British Journal of Cancer* 105, no. 9 (October 25, 2011): 1436–42.

Tsilidis, Konstantinos K., Naomi E. Allen, Timothy J. Key, Laure Dossus, Rudolf Kaaks, Kjersti Bakken, Eiliv Lund, et al. "Menopausal Hormone Therapy and Risk of Ovarian Cancer in the European Prospective Investigation into Cancer and Nutrition." *Cancer Causes & Control: CCC* 22, no. 8 (August 2011): 1075–84.

Tworoger, Shelley S., Kathleen M. Fairfield, Graham A. Colditz, Bernard A. Rosner, and Susan E. Hankinson. "Association of Oral Contraceptive Use, Other Contraceptive Methods, and Infertility with Ovarian Cancer Risk." *American Journal of Epidemiology* 166, no. 8 (October 15, 2007): 894–901.

Tzonou, A., A. Polychronopoulou, C. C. Hsieh, A. Rebelakos, A. Karakatsani, and D. Trichopoulos. "Hair Dyes, Analgesics, Tranquilizers and Perineal Talc Application as Risk Factors for Ovarian Cancer." *International Journal of Cancer. Journal International Du Cancer* 55, no. 3 (September 30, 1993): 408–10.

US EPA. "Health Assessment Document for Talc. | National Technical Reports Library - NTIS." -600/8-91/217, 1992.

Vallyathan, N. Val, Ph.D., et al. "Pulmonary Pathology in Workers Exposed to Nonasbestiform Talc." *Human Pathology*, Vol. 12, No. 1 (January 1981) 28-35.

Van Gosen, B. S., H.A. Lowers, S.J. Sutley, and C.A. Gent. "Using the Geologic Setting of Talc Deposits as an Indicator of Amphibole Asbestos Content." *Environmental Geology* 45, no. 7 (2004): 20.

Van Huisstede, A., et al. "Talcosis Due to Abundant Use of Cosmetic Talcum Powder." *European Respiratory Review*, Vol. 19, No. 116 (2010) 165-168.

Vanderhyden, Barbara C, Tanya J Shaw, and Jean-François Ethier. "Animal Models of Ovarian Cancer." *Reproductive Biology and Endocrinology: RB&E* 1 (October 7, 2003): 67.

VanOrden, D. "Weight Percent Compositional Analysis of Seven RTV Talc Samples. Analytical Report to R. T. Vanderbilt Company, Inc. Submitted to Public Comments Record – C. W. Jameson, National Toxicology Program, 10th ROC Nominations 'Talc (Containing Asbestiform Fibers)'. 4 December 2000., National Toxicology Program.," November 22, 2000.

Vasama-Neuvonen, K., E. Pukkala, H. Paakkulainen, P. Mutanen, E. Weiderpass, P. Boffetta, N.

Shen, T. Kauppinen, H. Vainio, and T. Partanen. “Ovarian Cancer and Occupational Exposures in Finland.” *American Journal of Industrial Medicine* 36, no. 1 (July 1999): 83–89.

Vasey, Paul A., Gordon C. Jayson, Alan Gordon, Hani Gabra, Rob Coleman, Ronnie Atkinson, David Parkin, et al. “Phase III Randomized Trial of Docetaxel-Carboplatin versus Paclitaxel-Carboplatin as First-Line Chemotherapy for Ovarian Carcinoma.” *Journal of the National Cancer Institute* 96, no. 22 (November 17, 2004): 1682–91.

Venkatesan, Priya. “Possible X Chromosome-Linked Transmission of Ovarian Cancer.” *The Lancet. Oncology* 19, no. 4 (April 2018): e185.

Venter, P. F., and M. Iturralde. “Migration of a Particulate Radioactive Tracer from the Vagina to the Peritoneal Cavity and Ovaries.” *South African Medical Journal = Suid-Afrikaanse Tydskrif Vir Geneeskunde* 55, no. 23 (June 2, 1979): 917–19.

Verdoodt, Freija, Christian Dehlendorff, Søren Friis, and Susanne K. Kjaer. “Non-Aspirin NSAID Use and Ovarian Cancer Mortality.” *Gynecologic Oncology* 150, no. 2 (2018): 331–37. https://doi.org/10.1016/j.ygyno.2018.06.018.

Vicus, Danielle, Amy Finch, Barry Rosen, Isabel Fan, Linda Bradley, Ilana Cass, Ping Sun, et al. “Risk Factors for Carcinoma of the Fallopian Tube in Women with and without a Germline BRCA Mutation.” *Gynecologic Oncology* 118, no. 2 (August 1, 2010): 155–59. https://doi.org/10.1016/j.ygyno.2010.03.009.

Vineis, Paolo, Phyllis Illari, and Federica Russo. “Causality in Cancer Research: A Journey through Models in Molecular Epidemiology and Their Philosophical Interpretation.” *Emerging Themes in Epidemiology* 14, no. 7 (2017).

Virta, RL. “The Phase Relationship of Talc and Amphiboles in a Fibrous Talc Sample.” IH; Report of Investigations, 1985. https://www.cdc.gov/niosh/nioshtic-2/10004328.html.

Vitonis, Allison F., Linda Titus-Ernstoff, and Daniel W. Cramer. “Assessing Ovarian Cancer Risk When Considering Elective Oophorectomy at the Time of Hysterectomy.” *Obstetrics and Gynecology* 117, no. 5 (May 2011): 1042–50.

Wang, Chunpeng, Zhenzhen Liang, Xin Liu, Qian Zhang, and Shuang Li. “The Association between Endometriosis, Tubal Ligation, Hysterectomy and Epithelial Ovarian Cancer: Meta-Analyses.” *International Journal of Environmental Research and Public Health* 13, no. 11 (November 14, 2016): 1138.

Wang, Dingzhi, et al. “Immunosuppression Associated with Chronic Inflammation in the Tumor Microenvironment.” *Carcinogenesis*, Vol. 36, No. 10 (2015): 1085-1093.

Wang, Xiaorong, Sihao Lin, Ignatius Yu, Hong Qiu, Yajia Lan, and Eiji Yano. “Cause-Specific Mortality in a Chinese Chrysotile Textile Worker Cohort.” *Cancer Science* 104, no. 2 (February 2013): 245–49.

Watson, Ian R., Koichi Takahashi, P. Andrew Futreal, and Lynda Chin. “Emerging Patterns of Somatic Mutations in Cancer.” *Nature Reviews. Genetics* 14, no. 10 (October 2013): 703–18.

Wehner, A. P., A. S. Hall, R. E. Weller, E. A. Lepel, and R. E. Schirmer. “Do Particles Translocate from the Vagina to the Oviducts and Beyond?” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 23, no. 3 (March 1985): 367–72.

Wehner, A. P., R. E. Weller, and E. A. Lepel. “On Talc Translocation from the Vagina to the Oviducts and Beyond.” *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association* 24, no. 4 (April

1986): 329–38.
Weiss, W. “Cigarette Smoking and Lung Cancer Trends. A Light at the End of the Tunnel?” *Chest* 111, no. 5 (May 1997): 1414–16.
Wells, I.P., et al. “Pulmonary Disease Caused By the Inhalation of Cosmetic Talcum Powder.” *British Journal of Radiology*, Vol. 52, No. 619; (July 1979) 586-588.
Wentzensen, Nicolas, Elizabeth M. Poole, Britton Trabert, Emily White, Alan A. Arslan, Alpa V. Patel, V. Wendy Setiawan, et al. “Ovarian Cancer Risk Factors by Histologic Subtype: An Analysis from the Ovarian Cancer Cohort Consortium.” *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology* 34, no. 24 (20 2016): 2888–98.
Werner, I. “Presence of Asbestos in Talc Samples.” *Atemschutzinform* 21, no. 5 (1982).
West, Sophie D., et al. “Pleurodesis for Malignant Pleural Effusions: Current Controversies and Variations in Practices.” *Curr Opin Pulm Med 10, Diseases in the Pleura*, (2004) 305-310.
Whiteman, David C., Michael F. G. Murphy, Linda S. Cook, Daniel W. Cramer, Patricia Hartge, Polly A. Marchbanks, Philip C. Nasca, Roberta B. Ness, David M. Purdie, and Harvey A. Risch. “Multiple Births and Risk of Epithelial Ovarian Cancer.” *Journal of the National Cancer Institute* 92, no. 14 (July 19, 2000): 1172–77.
Whittemore, A. S., R. Harris, and J. Itnyre. “Characteristics Relating to Ovarian Cancer Risk: Collaborative Analysis of 12 US Case-Control Studies. IV. The Pathogenesis of Epithelial Ovarian Cancer. Collaborative Ovarian Cancer Group.” *American Journal of Epidemiology* 136, no. 10 (November 15, 1992): 1212–20.
Whittemore, A. S., M. L. Wu, R. S. Paffenbarger, D. L. Sarles, J. B. Kampert, S. Grosser, D. L. Jung, S. Ballon, and M. Hendrickson. “Personal and Environmental Characteristics Related to Epithelial Ovarian Cancer. II. Exposures to Talcum Powder, Tobacco, Alcohol, and Coffee.” *American Journal of Epidemiology* 128, no. 6 (December 1988): 1228–40.
Whysner, J., and M. Mohan. “Perineal Application of Talc and Cornstarch Powders: Evaluation of Ovarian Cancer Risk.” *American Journal of Obstetrics and Gynecology* 182, no. 3 (March 2000): 720–24.
Wignall, B.K., and A.J. Fox. “Mortality of Female Gas Mask Assemblers.” *British Journal of Industrial Medicine* 39, no. 1 (1982): 34–38.
Wild, P. “Lung Cancer Risk and Talc Not Containing Asbestiform Fibres: A Review of the Epidemiological Evidence.” *Occupational and Environmental Medicine* 63, no. 1 (January 2006): 4–9.
Wolff, Henrik, Tapio Vehmas, Panu Oksa, Jorma Rantanen, and Harri Vainio. “Asbestos, Asbestosis, and Cancer, the Helsinki Criteria for Diagnosis and Attribution 2014: Recommendations.” *Scandinavian Journal of Work, Environment & Health* 41, no. 1 (January 2015): 5–15.
Wong, C., R. E. Hempling, M. S. Piver, N. Natarajan, and C. J. Mettlin. “Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study.” *Obstetrics and Gynecology* 93, no. 3 (March 1999): 372–76.
Woodruff, J. D. “The Pathogenesis of Ovarian Neoplasia.” *The Johns Hopkins Medical Journal* 144, no. 4 (April 1979): 117–20.
Wright, H. R., J. C. Wheeler, J. A. Woods, J. Hesford, P. Taylor, and R. F. Edlich. “Potential Toxicity of Retrograde Uterine Passage of Particulate Matter.” *Journal of Long-Term*

Effects of Medical Implants 6, no. 3–4 (1996): 199–206.
Wu, A. H., C. L. Pearce, C.-C. Tseng, and M. C. Pike. “African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates.” *Cancer Epidemiology Biomarkers & Prevention* 24, no. 7 (July 1, 2015): 1094–1100.
Wu, Anna H., Celeste L. Pearce, Chiu-Chen Tseng, and Malcolm C. Pike. “African Americans and Hispanics Remain at Lower Risk of Ovarian Cancer Than Non-Hispanic Whites after Considering Nongenetic Risk Factors and Oophorectomy Rates.” *Cancer Epidemiology, Biomarkers & Prevention: A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 24, no. 7 (July 2015): 1094–1100.
Wu, Anna H., Celeste L. Pearce, Chiu-Chen Tseng, Claire Templeman, and Malcolm C. Pike. “Markers of Inflammation and Risk of Ovarian Cancer in Los Angeles County.” *International Journal of Cancer. Journal International Du Cancer* 124, no. 6 (March 15, 2009): 1409–15.
Wu, Song, Wei Zhu, Patricia Thompson, and Yusuf A. Hannun. “Evaluating Intrinsic and Non-Intrinsic Cancer Risk Factors.” *Nature Communications* 9, no. 1 (August 28, 2018): 3490.
Yan, Bin, Yuanlin Peng, and Chuan-Yuan Li. “Molecular Analysis of Genetic Instability Caused by Chronic Inflammation.” *Methods in Molecular Biology (Clifton, N.J.)* 512 (2009): 15–28.
Yan, Bin, Huili Wang, Zahid Rabbani, Yulin Zhao, Wenrong Li, Yuqing Yuan, Fang Li, Mark W. Dewhirst, and Chuan-Yuan Li. “Tumor Necrosis Factor-a Is a Potent Endogenous Mutagen That Promotes Cellular Transformation.” *Cancer Research* 66 (December 15, 2006): 11565.
“You Can Steer Clients to Condoms Free from Potentially Harmful Talc: Condom Companies Agree to Produce without the Dry Lubricant.” *Contraceptive Technology Update* 16, no. 11 (November 1995): 133–44.
Zazenski, R., W. H. Ashton, D. Briggs, M. Chudkowski, J. W. Kelse, L. MacEachern, E. F. McCarthy, M. A. Nordhauser, M. T. Roddy, and N. M. Teetsel. “Talc: Occurrence, Characterization, and Consumer Applications.” *Regulatory Toxicology and Pharmacology: RTP* 21, no. 2 (April 1995): 218–29.
Zervomanoklakis, I, H.W. Ott, D Hadziomerovic, V. Mattle, B.E. Seeber, I. Virgolini, D. Heute, S. Kissler, G. Leyendecker, and L. Wildt. “Physiology of Upward Transport in the Human Female Genital Tract.” *Annals of New York Acadamy of Sciences* 1101, no. 1 (2007): 1–20.
Zhao, Weixing, Justin B. Steinfeld, Fengshan Liang, Xiaoyong Chen, David G. Maranon, Chu Jian Ma, Youngho Kwon, et al. “BRCA1-BARD1 Promotes RAD51-Mediated Homologous DNA Pairing.” *Nature* 550, no. 7676 (19 2017): 360–65.

DEPOSITIONS, TRANSCRIPTS AND REPORTS:

Affidavit of Laura Plunkett, PhD 02.22.18
Deposition of Alice Blount in the Ingham v. J&J Matter on 04.13.18
Deposition of Annie Awanais Yessian on 07.13.2017

Deposition and Exhibits of Pat Downey Dated 8.7.18-8.8.18
Deposition and Exhibits of John Hopkins Dated 8.16.18-8.17.18, 10.17.18 and 11.05.18
Deposition and Exhibits of Susan Nicholson Dated 7.26.18-7.27.18
Deposition and Exhibits of Julie Pier Dated 9.12.18-9.13.18
Ingham v. J&J Volume 11 (Egilman, Koman, Martinez, Packard) 6-14-18
Ingham v. J&J Volume 14A (Madigan, Williams) 6-20-18
Ingham v. JJ Volume 24A (Warner Huh, MD) 7.5.18
Ingham v. JJ Volume 24B (Warner Huh, MD) 7.5.18
John J. Godleski Expert Report for Brower Matter Dated 6.23.18
Lanzo Plaintiffs MIL re Imerys Spoliation and Concealment of Talc Samples
Laura Plunkett - Supplemental Expert Brower Report
Longo Analysis of J&J's Historical Talc Samples from the 1960's
Longo Analysis of J&J's Historical Talc Samples from the 1970's
Longo Analysis of J&J's Historical Talc Samples from the 1980's
Longo Analysis of J&J's Historical Talc Samples from the 1990's
Longo Analysis of J&J's Baby Powder Historical Samples - Asian - October 2018
Longo Analysis of J&J's BP Talc Products for Amphibole (Tremolite) Asbestos 8.2.17
Longo Analysis Report_Exhibit BB_04.28.2017
Longo MAS Project 14-1852 Below the Waist Application of Johnson's BP 9.2017
Longo Process Blanks for the Analysis of J&J's Products from the 60's to 90's for Asbestos
Longo TEM Analysis of Historical 1978 Johnson's BP Sample for Amphibole Asbestos 2.16.18
Longo Verification of Lee Poye's TEM Analysis of J&J's Historical Vermont Talc 11.5.18
Michael Crowley Expert Report Dated 11.12.18
Report of Results: MVA11730 Investigation of Italian Talc Samples for Asbestos 08.01.2017
RJLEE-001497
Thomas Dydek Brower Expert Report Dated 8.16.18 (corrected on 8.20.18)
Thomas Dydek Educational Report_FINAL (4-9-2018)
Thomas Dydek MDL Educational Report Dated 4.9.18

OTHER SOURCES:

American Cancer Society Ovarian Cancer Statistics
ATSDR Toxicological Profile for Asbestos
EPA Chemical Assessment Summary for Asbestos - 2017
EPA Guidelines for Carcinogen Risk Assessment - March 2005
EPA Health Assessment Document for Talc - 1992
Exhibit 1 - ATTORNEYS' EYES ONLY
Exhibit 2 - ATTORNEYS' EYES ONLY
Exhibit 3 - ATTORNEYS' EYES ONLY
FDA 4-1-2014 Response Letter to Epstein Denying Petition
Fitzgerald Analysis of J&J Baby Powder #1 and #2 Dated July 26, 2017
IARC Monograph 100C - Arsenic, Metals, Fibres, and Dusts - Excerpts
IARC Monograph 14 - Asbestos - 1977

IARC Monograph 2 - Some Inorganic and Organometallic Compounds - 1973
IARC Monograph 68 - Silica, Some Silicates, Coal Dust and Para-Aramid Fibrils - 1997
IARC Monograph 74 - Surgical Implants and Other Foreign Bodies - 1999
IARC Monograph 82 - Some Traditional Herbal Medicines, Some Mycotoxins, Naphthalene and Styrene - 2002
IARC Monograph 86 - Cobalt in Hard Minerals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide - 2006
IARC Monograph 87 - Inorganic and Organic Lead Compounds – 2006

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IMERYS045182
IMERYS045184
IMERYS048311
IMERYS051370
IMERYS053387
IMERYS090653
IMERYS098115
IMERYS105215
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IMERYS286445
IMERYS304036
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IMERYS340798
IMERYS342524
IMERYS406170
IMERYS422289
IMERYS 088907
IMERYS 284935
IMERYS137677-IMERYS137690
IMERYS209971
IMERYS241866
IMERYS248877
IMERYS255101
IMERYS255224
IMERYS255384
IMERYS255394
IMERYS255395
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IMERYS279968
IMERYS281335
IMERYS281776
IMERYS324700
IMERYS-A_0011817
IMERYS-A_0015663

J&J History
J&J S2s and BP Product Analysis - 1972
JNJ 000087928
JNJ 000088570
JNJ 000285351
JNJ000025132
JNJ000062359
JNJ000062436
JNJ000063608
JNJ000063951
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JNJAZ55_000008177
JNJL61_000014431
JNJMX68_000003728
JNJMX68_000012858
JNJMX68_000013019
JNJNL61_000079334
PCPC_MDL00062175
Pltf_MISC_00000272 (JANSSEN-000001-19)
NIOSH Occupation Respiratory Diseases September 1986
NIOSH Preliminary Report on Fiber Exposure During Use of Baby Powders - 1972
NTP Technical Report on the Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)- 1993
NTP Toxicology and Carcinogenesis Studies of Talc in F344/N Rats and B6C3F Mice Report No. 421
P-468
Read-the-Letter-from-the-FDA-on-Cosmetics
The Birth of Our Baby Products _ Kilmer House
WCD 002478 - Exhibit 32 Waldstreicher

Arch Carson, MD, PhD Legal Testimony, 2015-2018

Elaine Hale and Kenneth Dorsey parker, Jr. v. Centerpoint Energy Houston Electric, LLC; in the 55th District Court of Harris County, Texas.
2016 Harris County, TX for Plaintiff

Danny Henderson and Linda Henderson; Magdaleno Flores and Maria Flores; Shari Waldrop; and Bryan Thomas v. Magnablend, Inc., Nugreen Specialty, Inc., Nugreen Solutions, Inc., and Enviro Tech Inc.; in the 40th District Court of Ellis County, Texas.
2015 Ellis County, TX for Defendant

Edgar Guadalupe Solis v. Eastman Chemical Company, Texas Operations, Tradebe Environmental Services, Inc. d/b/a Tradebe Industrial Services LLC; in the 234th District Court of Harris County, Texas.
2015 Harris County, TX for Defendant

Arch I. Carson, MD, PhD
Professional Consultation Fee Schedule

Evidence-base research, report preparation, documentation, conference	$450/hr
Interview, physical examination or medical testing of patients	450/hr
Review of documents	450/hr
Testimony at deposition or trial plus expenses	450/hr
Inspection, examination or sampling of physical evidence or sites	450/hr
Travel (Travel maximum $4,000 per diem, plus expenses)	200/hr
Laboratory analyses/studies	at cost
Overhead and Supplies	at cost

Exhibit 52

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW) (LHG)**

RULE 26 EXPERT REPORT OF SONAL SINGH, MD, MPH

Sonal Singh

Date: November 16, 2018

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Sonal Singh, MD, MPH

TALCUM POWDER PRODUCTS AND RISK OF OVARIAN CANCER

EXPERT REPORT

Prepared by

Sonal Singh, MD, MPH

University of Massachusetts School of Medicine

Nov 16, 2018

Table of Contents

I. INTRODUCTION AND SUMMARY.

I have been retained to review scientific evidence and analyze the epidemiological data and, based on these data and other relevant evidence, to provide my professional opinion about whether talcum powder products are causally related to ovarian cancer. I have used a weight of evidence approach in examining the causal relationship between talcum powder products and ovarian cancer. I have relied upon my own systematic review of the literature and the cumulative body of evidence as the basis upon which I provide my opinions. This included gathering all relevant data based on *in vitro*, animal, and human epidemiologic studies on this topic. Although the weight of my opinions is derived from findings published in the peer-reviewed literature, relevant unpublished documents are also noted when applicable. The individual studies were examined for both reliability and validity noting their strengths and limitations. The cumulative body of evidence was then synthesized and examined and weighed using a widely accepted organizing framework- the Bradford Hill approach. (1). Using these materials, my education, and my prior clinical and research experiences, I have employed the methods generally accepted by the scientific community that would be used to develop a peer-reviewed manuscript.

In summary, it is my opinion, to a reasonable degree of scientific and medical certainty, that talcum powder products, specifically here Johnson's Baby Powder and Shower to Shower, can cause ovarian cancer. This finding is based on the totality of the medical and scientific evidence from meta-analysis, and consistent findings of a statistically significantly increased risk in observational studies, evidence of retrograde migration and inhalation of talc, presence of known or suspected carcinogens in Talcum Powder Products, and inflammatory tissue response that initiates multiple pathways and biological mechanisms by which talcum powder products can cause ovarian cancer While these factors carry the most weight in my assessment, available data on the biological gradient of Talc exposure and ovarian cancer (dose response) also support my opinion.

II. BACKGROUND AND QUALIFICATIONS.

I am an Associate Professor in the Department of Family Medicine and Community Health and the Meyers Primary Care Institute, with a joint appointment in the Department of Quantitative Health Sciences at the University of Massachusetts Medical School, Massachusetts. I received

my M.B.B.S. (equivalent to M.D.) in 1998 from Patna Medical College, India. I then completed my internal medicine internship and residency in the Department of Medicine at the Unity Health Center, affiliated with the University of Rochester School of Medicine in 2005. Subsequently, I served on the Faculty as an Instructor of Medicine at Wake Forest University until 2007, and then as an Assistant Professor of Medicine in 2007. I received a joint appointment as an Assistant Professor of Epidemiology at Wake Forest University in 2008. While on the faculty at Wake Forest University, I obtained my master's in public health at Johns Hopkins University in 2008. I was an Assistant Professor in the School of Medicine at Johns Hopkins University as a recipient of the NIH Johns Hopkins Clinical Research Scholars Award in 2009. I held joint appointments in the Department of International Health and Health Policy and Managements and served as the Associate Director at the Center for Drug Safety and Effectiveness at Johns Hopkins University until 2016.

In my current position, I devote most of my professional time to epidemiologic research. I conduct clinical research with a focus on drug safety, evidence synthesis, and shared decision making. The major focus of my research is understanding the adverse effects of pharmacologic therapies. The remainder of my professional effort is dedicated to practicing general medicine and teaching activities. I have taught courses in systematic reviews, clinical epidemiology, pharmacoepidemiology, and the practice of internal medicine to medical students, interns, residents, and public health students at Johns Hopkins University and Wake Forest University. I have taught courses in clinical epidemiology and pharmacoepidemiology to researchers in the Bloomberg School of Public Health at Johns Hopkins University

I have served as an advisor to the World Bank, WHO International Agency for Research on Cancer and various pharmaceutical firms. I was part of World Health Organization International Agency for Research (WHO-IARC) panel which evaluated the carcinogenicity of various drugs and herbal products. (2). I currently serve as a member of the American College of Chest Physicians Guideline Panel. I have also been part of a panel that developed the PRISMA-HARMS (Preferred Item for Reporting Harm in Systematic Reviews and Meta-Analyses) checklist with an aim to improve the reporting of systematic reviews and meta-analysis of adverse effects. (3). My research has been funded by the Food and Drug Administration, the Agency for Health Care Research and Quality, the National Institute of Health and the Patient Centered Outcomes Research Institute. I am a recipient of numerous awards including the prestigious Johns Hopkins Clinical Research Scholars Award from the

National Institute of Health and the Tinsley R. Harrison Master Teachers Award at Wake Forest University School of Medicine. My systematic review on varenicline and the risk of cardiovascular events published in the prestigious Canadian Medical Association Journal was awarded the Best Research Paper of the year among hundreds of articles submitted to the Journal. I also serve as a peer reviewer for more than 50 journals and serve on the editorial board of prominent journals such as *BMJ Evidence Based Medicine*. I have reviewed grants for numerous federal and international organizations. I have conducted several epidemiological studies and systematic reviews and meta-analysis featured in prominent medical journals such as the *Journal of the American Medical Association* and the *British Medical Journal*. I have authored or co-authored more than 100 original peer-reviewed scientific articles and my work has been cited more than 13,000 times and my h-index is 48 [h number of papers which has been cited by others at least h times]. My work has been featured in *Science, Journal of the American Medical Association, British Medical Journal, and the Lancet*, as well as media outlets such as the NYTIMES, *Wall Street Journal* and *Washington Post*.

This background provides experise in the use of epidemiological research methods in diverse settings, and in the clinical practice of medicine, both relevant to the present scenario. I have charged a rate of $600.00 per hour in the preparation of this report. Attached as Exhibit A is a copy of my curriculum vitae.

III. PUBLICATIONS.

Below is a representative sampling of those articles published in leading medical journals such as *Journal of American Medical Association, Journal of American Medical Association-Internal Medicine,* and *British Medical Journal*. Please refer to my attached curriculum vitae for a complete listing of all publications.

- Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone- A systematic review and meta-analysis. *Journal of the American Medical Association* 2007; 298: 1189-1195.
- Singh S, Loke YK. Furberg CD. Inhaled anticholinergics and the risk of major adverse cardiovascular events in Patients with Chronic Obstructive Pulmonary Disease: A systematic Review and Meta-analysis. *Journal of the American Medical Association* 2008; 300: 1439-1450. (CME Article in JAMA).

- Mills EJ, Wu P, Chong G, Ghement I, Singh S, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170 255 patients from 76 randomized trials. Q J Med 2011; 104: 109-24.
- Singh S, Loke YK, Enright P, Furberg CD. Mortality Associated with Tiotropium Respimat® in Patients with Chronic Obstructive Pulmonary Disease- A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *British Medical Journal* 2011; 342: d3215.
- Singh S, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events with Varenicline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Canadian Medical Association Journal* 2011; 1831359-66. (with an editorial by JT Hays. Varenicline for smoking cessation. Is it a heart breaker?)- Best Research paper of the year award.
- Singh S, Loke YK. Drug Safety Assessment in Clinical Trials: Methodologic Challenges and Opportunities. Trials 2012, 13: 138.
- Singh S, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Ovarian cancer Mellitus: A Population-Based Matched Case-Control Study. *Journal of the American Medical Association Intern Med*. 2013 25:1-6.
- Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, Singh S, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol*. 2013; 14(9):807-8.
- Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., Singh S, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *British Medical Journal* 2016;352: i157.
- Onasanya O, Iyer G, Lucas E, Lin D, Singh S, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 Nov;4(11):943-956.
- Alexander GC, Iyer G, Lucas E, Lin D, Singh S. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 Dec;130(12):1449-1457.

IV. STUDY DESIGN CONSIDERATIONS.

I will examine the strengths and weaknesses of the study designs that are relevant to the present scenario. Each of the study-types discussed below has its advantages and disadvantages. Every study is subject to biases and error; none is appropriate and feasible for every situation. Instead, the evidentiary value of each study must be assessed and weighed on an individual basis, and in the context of the totality of the body of literature or scientific studies.

IV.I Randomized controlled trials. In double blind randomized controlled trials (RCTs) both the investigator and the participant are blinded to treatment assignment. All characteristics whether known or unknown, are evenly distributed at random between the intervention and placebo arm. Thus, if there are differences in incidence of outcome, it can be inferred to be a consequence of the exposure itself (i.e. causative).

However, the prospective nature of RCTs also results in several significant drawbacks for effects that are rare and/or slow to develop, like ovarian cancer. In addition to the ethical difficulties of administering a substance that may be harmful, such as talcum powder products, it is difficult prospectively to ensure study-subject compliance over the decade-plus timeframes required to assess ovarian cancer risk, and obviously impractical to have researchers administer a daily perineal talc application to study subjects. Similarly, there is no mechanism by which to randomly assign participants for non-modifiable exposures or the event may be sufficiently rare, such as in the present case of ovarian cancer to be evaluated in a randomized trial. The definitive randomized controlled trial in which patients would be randomized to talcum powder products and/or placebo and measure the outcome of ovarian cancer would be ideal. However, such a randomized trial does not exist, and such a randomized trial would be unethical.[1] Then again, randomized clinical trials are not necessary to establish causal evidence of harm. For instance, there is no randomized trial which supports the causal role of smoking in lung cancer. As a result, to address this question, we must rely on other study designs including observational studies and their meta-analysis to draw inferences on causation. The preponderance of evidence we have on harms of products are derived from such epidemiological studies.

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[1] Defendants here have admitted this fact. Deposition of Linda Loretz 562:14-563:6 (October 1, 2018) (4); Deposition of Joshua Muscat 408:21-410:20 (September 25, 2018) (5).

IV.II Systematic reviews and Meta-analysis. A systematic review and meta-analysis is a study design wherein systematic searches are carried out to identify studies reporting on a question of interest. Systematic reviews provide a high level of evidence when evaluating the effect of interventions. (6).

The meta-analytic point estimate represents the sum of evidence from all the included studies. When individual studies may be underpowered to detect an effect, meta-analysis of cumulative studies may allow one to distinguish whether the entire body of evidence supports the presence or argues against evidence of a causal association. Apart from the P-value as a measure of statistical significance, the confidence intervals are used to assess the statistical variability around the estimate. In a meta-analysis the studies are weighted by the sample size of included studies with larger studies contributing more weight to the final estimate. Studies are examined to determine whether the findings are clinically and statistically homogenous or heterogenous. Clinical heterogeneity includes any differences in populations and interventions. It is also important to evaluate statistical heterogeneity among studies included in the meta-analysis. (7). Although some amount of variation in individual estimates of treatment effect is expected by chance, the excess of variation which cannot be explained by chance alone is referred to as statistical heterogeneity. I^2 is used as a measure of *statistical heterogeneity*—a percent of variation due to heterogeneity compared to chance, the higher the value the more the proportion of statistical heterogeneity.

The different approaches to modelling data across studies may yield slightly different results. Fixed effects meta-analysis which assumes that all the studies are measuring the same effect yield tighter confidence intervals, whereas random effects meta-analysis which assume that studies are measuring different effects in the population yield more conservative effects. Random-effects models may be more appropriate when the amount of statistical heterogeneity is high. Some amount of heterogeneity is expected when the database includes observational studies.

However, it must be noted that while meta-analysis can overcome issues of limited statistical power and provide information on consistency or inconsistency of effects, one needs to carefully examine the individual studies for their limitations and susceptibility to bias and confounding.

Thus, for example, if a study is too short to detect the effect in question, then even a patient-level pooled analysis of several such studies will very likely fail to detect a true causal relationship, even when one exists. This is an illustration of why it is important to consider study design, bias, and confounding in weighing the results from both individual studies and their meta-analysis. Systematic reviews are also susceptible to various publication and funding biases which need to be considered in interpreting results.

Meta-regression in using summary or group level published data may be susceptible to ecological or group level biases and result in spurious conclusions. (8). As a result, it is not recommended to evaluate the association between treatment effect, such as the difference in the risk of ovarian cancer, and participant characteristics at the study level (e.g., mean age of all participants) using aggregate level data, (9) as these may be susceptible to group level or ecological biases. An individual participant pooled analysis in which investigators have access to the patient-level data, such as that by Terry et al. discussed below, (10) is considered of higher quality than meta-analysis of summary data and provides the ability to reliably assess the effect of other patient and outcome related variables.

Umbrella reviews and overviews of systematic reviews. An umbrella review systematically collects and reviews evidence from multiple systematic reviews and meta-analysis and allows integration of evidence from multiple systematic reviews and meta-analysis, (11) to offer a much broader view of the evidence landscape. Individual systematic reviews and/or meta-analysis included in an umbrella review or overview should be critically appraised for quality. The 11-item critical appraisal tool AMSTAR (Assessing the Methodological Quality of Systematic Reviews) is a reliable and valid tool which provides an assessment of the quality of included systematic reviews and meta-analysis in an overview. (12).

What is the precise causal question or the hypothesis being tested? One cannot interpret the scientific evidence without being precise about the causal question that is being addressed when evaluating the association between any exposure and an outcome in any epidemiologic study. An exclusively narrowly framed hypothesis (e.g., evaluating only one route of exposure such as using talcum powder on contraceptive diaphragm), (13) while disregarding other important and relevant routes and mechanisms of exposure, is <u>inherently limited by design.</u> Since we may not have a complete picture of the underlying mechanisms or the timings of risk of products at the

time of study design, it is even more critical that studies on safety evaluate all potential routes of exposure.

IV.III. Cohort and Case-Control Studies. There are several considerations in interpreting data from prospective or retrospective observational studies or case-control studies. However, it is important to consider issues of study design, random error, systematic error, bias, and confounding in the interpretation of data. Random errors are statistical fluctuations in the measured data due to the limitations of the measurement instrument. They may occur in both direction because of the inability to measure exposure and outcomes in precisely the same manner. There is also the possibility of measurement error in the measurement of outcome and exposure in both study designs. If the measurement error is non-differential, such misclassification of exposure or outcomes usually biases findings towards the null. Systematic errors, by contrast, are reproducible inaccuracies that are consistently in the same direction, often due to a problem which persists throughout the entire study and are difficult to correct.

Case-control studies involve subjects diagnosed with the disease at issue, such as ovarian cancer (the “cases”), and a suitable number of subjects without the disease (the “controls”). Exposure is ascertained retrospectively among both cases and controls. The results are then analyzed to see if there is an association between the exposure and the disease. In contrast, prospective cohort studies are study designs in which subjects with and without the exposure of interest are recruited and followed up in time for the development of outcomes. This study design establishes temporality wherein the exposure precedes the outcome. It is important to determine the latency and induction between the exposure and the disease to assess the duration of follow-up. As an example, a 12-month follow-up study to evaluate the association between exposure to smoking and lung cancer would be unlikely to demonstrate an increase in the risk of lung cancer.

There are several strengths to the case-control design including the ability to ascertain long-term exposure-outcome relationships, particularly important to the present scenario because ovarian cancer develops over many years. Once cases and controls have been established, one can evaluate the association between multiple exposures and outcomes. In contrast, prospective cohort studies may be limited by the short-duration of follow-up which may be insufficient to ascertain the effect of exposure on long-term outcomes and bias their findings towards the null. Secondly, for relatively rare diseases, such as ovarian cancer, case-control studies are more

efficient. Because we are looking at the incidence of disease between the two arms of a study, a cohort study may have limited statistical power regardless of the actual number of subjects enrolled if the number of cases is small. For example, the Nurses' Health Study recruited almost 80,000 participants for only 307 cases of ovarian cancer. (14).

Both study designs are susceptible to selection bias when the selection of the participants into the study (or their likelihood of being retained in a cohort study) leads to a result that is different from the result had we enrolled the entire target population. In other words, the exposure-outcome relationship in controls or cases may be different from the target population. This can arise due to selection of controls not representative of the target population, non-response that is related to exposure and outcome, or differential loss to follow-up in a cohort study related to exposure and outcome status. Selection bias can bias findings either away from the null or towards the null.

Case-control studies, by their design, are generally not blinded and are also susceptible to bias as a result. They are also susceptible to recall bias, i.e. the concern that subjects with the disease may be more diligent in recollecting past uses. However, the degree of recall bias will depend on the type of exposure with chronic daily long-term exposures, such as talcum powder product use, being less likely to be subject to recall bias than intermittent short-term exposures. In contrast, prospective cohort studies in which subjects are recruited and then followed up for the development of outcomes are less susceptible to recall bias.

In addition, there is the issue of what may be called "behavior change" bias in cohort studies which may also bias their findings towards the null if exposure is only ascertained at baseline and not updated during follow up. This bias towards the null reduces the apparent effect of the exposure on the outcome. For example, if the subjects accurately report their talcum powder product use (or lack there-of) at baseline, but there is no follow-up, then the "ever" users' status will still be correct at the end of the study, because once having used talc, their "ever" status cannot change. This will not be true, however, of the "never" users; if they subsequently use talc, then without follow-up, their status will still be incorrectly recorded as "never." If there is a true causal connection, some ovarian cancers caused in the "never" category will, in fact, belong in the "ever" category, potentially biasing the study towards the null. Cohort studies are also susceptible to attrition bias and efforts should be used to minimize loss to follow-up. The main strengths of cohort studies are that if an effect (after adjusting for other confounding

factors) is found despite these biases towards the null, then it is more likely to be a causal relationship; the limitations being that they are less sensitive to determining a causal relationship. Case-control studies are based on past behavior and are not affected by this bias. Cohort studies are also susceptible to several prevalent user biases including potential bias due depletion of susceptibles. (15). A cohort study evaluating the association between talc use and ovarian cancer which limits the analysis to prevalent users (rather than new users), may largely be composed of survivors of the early effect of talc exposure on ovarian cancer, since new users who developed ovarian cancer after talc exposure may be ineligible for inclusion. This will potentially bias the estimates towards the null.

One important distinction to note is between risk factors for the disease and confounders. (16). A risk factor is an exposure which may explain the development or cause of disease in the population. These could be potentially modifiable or non-modifiable risk factors such as genetic risk factors. Confounding represents a special case of bias that results when the relationship between the risk factor -disease relationship is altered. A variable is considered a confounder only when ALL three criteria are present: a) the confounder is associated with the exposure in the population; b) the variable is related to the disease in the population; and c) the variable is not a link in the causal pathway to the disease. Risk factors that do not meet all the above criterion are not considered confounders of the exposure-outcome relationships (and thus may not require adjustment in the analysis).

Observational studies may also be susceptible to unmeasured confounding. Importantly, the potential for confounding does not mean that such a confounding exists. To address bias, confounders of the disease-outcome relationship need to be adjusted for in the analysis of epidemiologic studies. The methods for adjustment for known confounders include regression or propensity score methods. In establishing the effect of any exposure on an outcome it is important to disentangle the direct effect of an exposure of an outcome vs the indirect effect because of some mediators. The strength of association, in and of itself, does not denote whether a risk factor causes the disease. It is reflective of the background rate of the disease in the population and the relative risk of other competing risk factors. When the strength of association is weak, restricting the disease to a low risk population with low background rates of the diseases will magnify the association due to lack of competition among risk factors. (16)

One must be careful in interpreting data from subgroup analysis, such as analysis of various dose categories or age or ethnic groups, such as the case here with pre-menopausal women vs post-menopausal women or subgroup of women stratified by age, sex and ethnicity. The results of tests of interaction are important in interpreting data from such studies. If the test of interaction is not significant, this suggests that there is a lack of significant difference between the two groups. However, such subgroup tests can be underpowered because of reduction in sample size. Additionally, while a study may be internally valid it may not be generalizable to participants in the overall population beyond those included in the study. As an example, the cohort study of post-menopausal women reporting a non-significantly increased risk of ovarian cancer with genital talc use may not be generalizable to premenopausal women. (17). Despite the limitations noted above, most of our knowledge of the adverse effects of therapies has been derived from observational studies, since randomized controlled trials are not practical for several agents and rare outcomes.

It is also important to draw attention to the proper interpretation of P-values, confidence intervals and statistical significance. (18). I have followed the general principles laid out by the American Statistical Association on the interpretation of P-values and statistical significance. P-value can only indicate how incompatible data are with a statistical model. P-values do not indicate the probability that the studied hypothesis is true or the probability that data were produced by random chance alone. A P-value does not measure the size of an effect or the importance of a result and undue reliance should not be placed on whether a P-value passes a specific threshold. Full reporting and transparency are needed for interpretation of results. Confidence intervals (CI) measure statistical significance, (19) and indicate the precision and degree of uncertainty associated with a sample statistic. A 95% CI means that if we used the same sampling method to select different samples and computed an interval estimate for each sample, we would expect the true population parameter to fall within the interval estimates 95% of the time. CIs that remain elevated above 1 for relative risks (RRs) or odds ratios (ORs) are considered statistically significant. A narrow CI indicates a relatively higher level of precision. Non-overlapping CIs across two studies suggest a statistically significant difference between the study findings, whereas overlapping CIs may suggest consistent results. Thus, it is not necessary, and it is highly unlikely to have identical point estimates across studies to establish the presence of a consistent exposure-outcome association.

V. EPIDEMIOLOGY AND PATHOGENESIS OF OVARIAN CANCER.

Ovarian cancer is the most lethal gynecologic cancer in women. It is the leading cause of cancer death among gynecologic cancer in the US and the fifth most common cause of cancer with more than 14,000 deaths per year. The incidence is 11.4 cases per 100,000 women per year, with a mortality rate of 7.4 deaths per 100,000 women. (20). Approximately 1.3 percent of women will be diagnosed with ovarian cancer at some point during their lifetime. Approximately 22,400 new cases of ovarian cancer would be diagnosed in the US in 2017 with 14,080 deaths. (21).

Most women are diagnosed at an advanced stage of the disease and it is usually asymptomatic but may present as abdominal distention, bloating, and in a minority of cases vaginal bleeding. The prognosis is relatively poor when it presents at the advance stage where therapeutic options including chemotherapy offer little benefit. As discussed in more detail in Section X below, inflammation is known to play an important role in the pathogenesis of ovarian epithelial cancer through a mechanism of cell proliferation, oxidative stress DNA damage and gene mutations.

VI. WHAT CONSTITUTES COSMETIC TALCUM POWDER PRODUCTS?

- While I will examine the evidence of talcum powder products and their causal association with ovarian cancer, ascertaining what constitutes "talcum powder" it is important to emphasize that Talcum powder cosmetic products are not "pure talc." The evidence I reviewed demonstrates talcum powder products contain asbestos, fibrous talc, heavy metals such as cobalt, chromium, nickel, and various fragrance chemicals (22)(23). This report evaluates the risk of ovarian cancer associated with talcum powder products and its constituents. When I refer to talc or talcum powder products in this report, I am referring to commercially available talcum powder products and all constituent elements contained within.

- Talc is a naturally occurring mineral and its chemical composition is hydrous magnesium silicate with a chemical formula of $Mg3Si4O10(OH)2$. In its natural form, talc may contain asbestos, also a naturally occurring silicate mineral, with a different crystal structure. Both talc and asbestos belong to the family of silicates that may occur in fibrous form, which is known to cause cancer. The structure of talc is characterized by a hexagonal sheet arrangement of silicon oxygen tetrahedral groups in a common plane. This results in a double-sheeted structure where the sheets are held together by weak van der Waals bonds. Talc consists mostly of these plate-

like structures ("platy talc") but talc can occur in fibrous form. Talc fibers are like asbestos fibers in size and shape. (22, 24).

- Despite claims that talcum powder products manufactured after the mid-1970s were "asbestos free," published articles, internal company documents, and testing of historical samples I reviewed demonstrate that talcum powder products can contain asbestos and other carcinogenic constituents as discussed below. For example, talc powders from national and international markets were analyzed by Paoletti et al. in a 1983 study to assess fiber content. (25). Samples of talc powders demonstrated fiber contents up to 30% of total particles. About half of the talc powders revealed the presence of asbestos. In some samples, a very high level of asbestos was revealed. (25). Consistently, the 1991 Blount study also found asbestos in cosmetic talcum powder. (26). In a recent deposition, the author of the 1991 study testified she had detected specifically in Johnsons and Johnsons baby powder. (27).

- Although the FDA conducted a survey of talc manufacturers in 2009-2010 and found no asbestos fibers or structures in any of the samples of cosmetic-grade raw material talc or cosmetic products containing talc, (28) the results were limited; only four out of nine talc suppliers submitted samples, and the number of products tested was low. The failure to detect asbestos could either be due to the technique used or the use of a non-representative sample. The FDA itself noted the study could not "prove that most or all talc or talc-containing cosmetic grade products currently marketed in the United States are likely to be free of asbestos contamination." (29).

- I reviewed Longo et al.'s report from August 2017 where he tested 30 bottles of Johnson's Baby Powder. (30). They found 17 samples contained detectable amounts of asbestos. They also found half of the samples contained fibrous talc. I also reviewed two additional reports from Dr. Longo where he found fibrous talc and asbestos in Johnson's Baby Powder. (31, 32). I reviewed the depositions and exhibits of Dr. John Hopkins, corporate representative for Johnson and Johnson, who testified to numerous positive tests for asbestos and fibrous talc. (33).

- In a recent report, Longo et al. (34) estimates that 37 out of 56 random samples (66%) of bottles of talcum powder products tested contain asbestos, which indicates that approximately 2 out of 3 bottles of talcum powder containing products are contaminated with asbestos. Talcum powder products are generally used by women habitually for months or years, rather than a

single application or a single bottle of use. Each successive use of a bottle of talcum powder product_by an individual further accentuates the cumulative probability of their exposure to asbestos, beyond the probability conferred by the use of a single bottle. I reserve the right to supplement my report in order to estimate this probability of exposure to asbestos through habitual use of talcum powder products contaminated with asbestos, once the analysis of additional samples of talc is complete. Longo et al. also estimates that 41 of 42 random samples of bottles of talcum powder products tested contain fibrous talc. I reserve the right to supplement my report in order to estimate this probability of exposure to fibrous talc through habitual use of talcum powder products contaminated with fibrous talc, once the analysis of additional samples of talc is complete.

- I also reviewed the deposition and exhibits of Julie Pier, corporate representative for Imerys Talc America, Inc., who testified to numerous positive tests for asbestos and heavy metals between 1985 and 2002. (35).

- My review of monographs published by the International Agency for Research on Cancer (IARC) show that asbestos is a well-established carcinogen and unequivocally known to cause several cancers including mesothelioma of the lung, larynx, and ovarian cancer. (36). Overall, the International Agency for Research on Cancer Working Group classified asbestos compounds as "carcinogenic to humans" (Group 1) in 2012. (36, 37). IARC has also concluded that talc including asbestiform fibers grown in an asbestiform habit - commonly termed "fibrous talc" - is "carcinogenic to humans" (Group 1). (38).

- I also reviewed documents demonstrating talcum powder products may contain heavy metals such as chromium, nickel, and cobalt. (22). Asbestos, chromium, and nickel were all classified as a Group 1 carcinogens by IARC. (36) Cobalt is also present in talcum powder products and classified by IARC as a Group 2B carcinogen.

VII. SUMMARY OF OPINIONS.

1. **Statistical Significance**. There is a statistically significant increased risk of ovarian cancer with talcum powder products as demonstrated by most meta-analyses to date. (10, 39-42). Although a flawed analysis conducted limited to the use of talc dusted diaphragms and ovarian cancer conducted on behalf of the manufacturer reported an excess risk which was not

statistically significant, (13) it had several data extraction errors and was of lower methodological quality. (43). Several independent meta-analysis by academic researchers, some of which include individual participant data, (10) and the most recent meta-analysis reported a statistically significantly increased risk of ovarian cancer associated with perineal talc use, (42) rendering the previous findings of Huncharek et al obsolete. The studies of the highest rated methodologic quality as shown in **Table 1** which provides a methodologic grading of the quality of the included systematic reviews using the AMSTAR checklist have reported a statistically significantly increased risk of ovarian cancer associated with genital talc use. (10, 41, 42). See Section IX.IV for a summary of findings from epidemiological studies.

2. **Consistency and Replication**. These findings of a statistically significantly increased risk of ovarian cancer with talc use have been consistently replicated by several independent investigators in different population, and different settings across different data sources using different study designs. These slight differences in magnitude of risk reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time. The meta-analysis of case-control studies has consistently shown a statistically significantly increased risk, whereas the meta-analysis of cohort studies has also shown an excess risk, (42) which failed to reach statistical significance, due to inadequate statistical power and low number of events; but the confidence intervals of results between the two study designs overlap providing evidence of consistency. The number of ovarian cancers in the case-control studies exceeds the number of ovarian cancers in the cohort studies by several fold. (42).

3. **Strength of Association**. The cumulative strength of association for the increased risk of ovarian cancer associated with talcum powder containing products is significant and ranges from 30 % to 60% %. The strength of association is similar to estimates of other established carcinogens (e.g., 24 % increased risk of lung cancers in non-smokers exposed to environmental tobacco smoke) (44), hormone replacement therapy and breast cancer (RR 1.33, 95% CI: 1.24-1.44) (45), particulate matter and lung cancer (PM2.5: RR 1.09, 95% CI: 1.04, 1.14 and PM10: 1.08, 95% CI: 1.00-1.17). (46). Beyond carcinogens, there are well established examples of causal associations in epidemiology, such as in the case of particulate matter and myocardial infarction, where the statistically significant excess risks are in the order of even less than a percent (carbon monoxide: 1.048, 95% CI: 1.026-1.070; nitrogen dioxide: 1.011, 95% CI, 1.006-1.016; sulfur dioxide: 1.010, 95% CI: 1.003-1.017; PM(10): 1.006, 95% CI: 1.002-1.009; and PM(2.5): 1.025, 95% CI: 1.015-1.036 and ozone: RR 1.003, 95% CI: 0.997-1.010; P = .36). (47).

4. **Exposure-Response Assessment.** The assessment of exposure–response or biological gradient is hindered by the difficulty in quantifying talcum powder use usually collected by

self-reported data (frequency, amount, and duration), timing and patterns of use (e.g., douching), and other individual factors (e.g., co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. As discussed in the dose-response summary of epidemiological studies below, some studies have measured the frequency of exposure, others the duration of exposure with few studies measuring the combined duration and frequency or intensity of exposure. (48). It is important to interpret the exposure-response data in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer through alteration of the redox state in epithelial ovarian cancer cells, (49) and a monotonic dose-response curve may not accurately reflect this mechanism of development of ovarian cancer mediated via inflammation and alterations in redox states. Some epidemiologists have argued that it is difficult to know how dose-response should be modelled and it is unclear why nature would mandate a monotonic dose-response gradient. (50). Although it is difficult to know how to model the talc-ovarian cancer exposure-response assessment, it is possible that an agent which accelerates the development of cancer could account for threshold effects rather than monotonic dose-response effect. Despite these challenges, I address studies which have shown evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 57). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis reported an increased risk with >3600 lifetime applications compared to <3600 lifetime applications of perineal talc based on data from case-control studies. (42). A limited number of studies have shown no evidence of dose-response either with increased frequency or duration of exposure. (58-60).

5. **Retrograde Migration of Talc and Routes of Talc Exposure.** Talcum powder particles can migrate to the fallopian tubes and ovaries. (61-63). Talc and/or other constituents have been detected within the ovaries of women who report perineal talc use, (64) and found deeply embedded within ovarian tumors. (62, 65). Talc has also been reported in the lymph nodes which could occur through migration absorption or inhalation with transport through the lymphatic system. (66). Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc" in unrelated monkey models, (67) the timing and techniques of assessment and intraspecies differences could not completely rule out migration of talc particles. Furthermore, supportive evidence for migration comes from the findings of a decreased risk of ovarian cancer with tubal

ligation and hysterectomy, (62) evidence of migration of other particles such as starch. (68). The FDA concluded that the "potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable." (69). A secondary route of exposure is inhalation. (36, 70).

6. **Multiple Biological Mechanisms of Talc Induced Ovarian Cancer.** Although not an absolute requirement for demonstrating causality, there is strong evidence that talcum powder products can induce ovarian cancer through established biological mechanisms (Section X). (39, 49, 71, 72). Inflammation plays a leading role in ovarian cancer and talc has pro-inflammatory effects; it also induces alterations in redox potential and pro-oxidant effects. (49) In ovarian cells talc has been shown to increase proliferation, increase neoplastic transformation and increase reactive oxygen species in the ovarian cells. (71). Talc has also been shown to be mutagenic in human ovarian epithelial cells through increased activation of gene activating transcription factors. Finally, the presence of asbestos and other Group 1 carcinogens likely contributes to the carcinogenicity of talcum powder products, and provides biologic plausibility for the consistent and significant increased risk seen in the epidemiologic studies on Talc and Ovarian cancer.

VIII. METHODS FOR THE OVERVIEW OF SYSTEMATIC REVIEW OF OBSERVATIONAL STUDIES OF GENITAL TALC USE AND OVARIAN CANCER.

I conducted an overview of systematic reviews and meta-analysis of observational studies of genital talc use and ovarian cancer. I included systematic reviews regardless of the performance of quantitative synthesis as meta-analysis may occasionally not be performed for data from observational studies. To inform the causal question, I also evaluated additional studies which provided evidence on the causal question of whether talcum powder products induce ovarian cancer. I critically appraised the meta-analysis using the 11- item AMSTAR (Assessing the methodologic quality of Systematic Review) checklist for systematic reviews and meta-analysis. (12) The individual epidemiological studies were also evaluated and summarized for their key strengths and limitations.

VIII.I. Systematic search. I performed an initial systematic search of Scopus and PubMed with the following search terms on June 12, 2017:

Pubmed: ("talc"[MeSH Terms] OR "talc"[All Fields]) AND ("ovarian neoplasms"[MeSH Terms] OR ("ovarian"[All Fields] AND "neoplasms"[All

Fields]) OR "ovarian neoplasms"[All Fields] OR ("ovarian"[All Fields] AND "cancer"[All Fields]) OR "ovarian cancer"[All Fields])

Scopus: (TITLE-ABS-KEY (talc) AND TITLE-ABS-KEY (ovarian AND cancer)

VIII.II Eligibility Criteria. I included and considered epidemiological studies, including case-control studies, cohort studies and systematic review and meta-analysis which reported on the association between talc and ovarian cancer. I searched the references of included studies and citing articles to find additional original articles. I also included in vitro, animal, and human epidemiologic studies that reported data that either support or refute the role of talc in the development of ovarian cancer. I excluded duplicate articles identified in the two databases, articles with no original data, narrative reviews, commentaries and opinion pieces , and citations not relevant to the present scenario. The title and abstracts of each manuscript were reviewed to identify potential studies for inclusion in this report. I also searched the reference of included studies to find relevant citing articles. New studies were identified after evaluating citing articles. I reviewed the full length of each of these manuscripts and provide a summary of their key findings below.

IX. RESULTS.

The results of the initial search yielded 273 citations. I included 9 studies in the section on overview of systematic reviews and meta-analysis. (10, 13, 39-42, 57, 73, 79). I also assessed the 29 case-control studies, (48, 51-60, 62, 66, 75-91) and 3 cohort studies (14, 17, 92-93). The list of excluded citations is shown. The difference in the citation count of included and excluded articles largely reflects excluded duplicate articles retrieved from the two databases. I also evaluated several studies (36, 37, 49, 64-68, 72, 94-109) which reported on the biological mechanisms that supported or refuted the causal association between talcum powder products and ovarian cancer.

IX.I. Overview of Systematic Reviews and Meta-analysis. Three meta-analysis were not preceded by a systematic search (57, 73, 79). There were 4 systematic reviews and meta-analysis which evaluated the link between perineal talc use and ovarian cancer (39-42) using summary data, while an individual participant data analyses pooled data from case-control studies in the Ovarian Cancer Consortium (10). Another systematic review and meta-analysis analysis conducted on behalf of the manufacturer only evaluated the use of cosmetic talc on

contraceptive diaphragms and ovarian cancer (13) and was not directly relevant to the causal question of genital talc use and the development of ovarian cancer, but was critically evaluated for strengths and weaknesses. The results of the methodologic assessment of each of these using the AMSTAR checklist is summarized in the Table 1. Two meta-analysis (13, 40) are of poor methodological quality. Regardless, the findings of older meta-analysis have been superseded given the publication of new meta-analysis. (41, 42).

1. In 1992, Harlow et al. combined crude odds ratios from their case-control study, discussed below with 5 pre-existing existing case-control studies (79) to evaluate the association between perineal talc exposure and ovarian cancer. The studies included 1106 cases and 1756 controls, with talc exposure reported among 50.7% of cases and 46.9% of controls. Using crude odds ratios from the individual studies, perineal exposure to talc was associated with a statistically significantly increased risk of ovarian cancer (OR 1.3, 95% CI: 1.1-1.6). Major limitations include the lack of a systematic search methodology.

2. A 1995, meta-analysis by Gross and Berg (39) was conducted on behalf of the manufacturer Johnson and Johnson. A search of PubMed issuing the terms "ovarian cancer" and "talc or cosmetic" identified 9 case-control studies and reported a statistically significant increased risk of ovarian cancer in both the crude odds ratio (1.27, 95% CI: 1.09-1.48) and adjusted odds ratio (1.31, 95% CI: 1.08-1.58). They also examined the odds ratio by tumor type and notes that all the analyses produced relative risks greater than 1 with confidence intervals that exceeded 1. Despite the statistically significantly increased risk seen in analyses, the authors concluded that the *"literature does not unequivocally support the hypothesis…. But [does] suggest the possibility of an increased risk of ovarian cancer due to perineal talc use."* The description of study procedures was incomplete, and the search strategy was limited. The study was supported in part by the manufacturer.

3. Cramer et al. 1999 combined crude odds ratio data from their case-control study with pre-existing case-control studies in a meta-analysis of 14 total case-control studies, (57) and reported a statistically significant OR of 1.36 (95% CI: 1.24-1.49). The tests for statistical heterogeneity were not significant (p=0.085). Limitations include the lack of a systematic search.

4. Huncharek, for his 2003 publication, conducted a meta-analysis of 16 studies including 11,933 subjects. (40). They searched MEDLARS, Embase and Cancer Lit databases using search term "talc exp ovarian neoplasms." They excluded studies on borderline tumors or those which did not report on types of perineal exposure (dusting vs sanitary napkins). The meta-analysis was conducted using adjusted measures of effect using the inverse variance method. It included 15 population-based and 1 hospital-based study and excluded the 1983 Hartge study. (76). The pooled analyses yielded a significantly increased risk of ovarian cancer (RR 1.33, 95% CI: 1.16-1.45) associated with the perineal use of talc without evidence of statistical heterogeneity. Seven studies reporting on the number of talc applications per month were evaluated where the highest risk category (RR 1.21, 95% CI: 1.00-1.45) and lowest risk category (RR 1.83, 95% CI: 1.55-2.15) reported an increased risk. In sensitivity analyses, hospital-based studies showed no statistically significant excess risk between talc use and ovarian cancer risk, i.e., RRs 1.19 (95% CI: 0.99-1.41) versus population-based studies which showed an increased risk (RR 1.38, 95% CI: 1.25-1.52), despite the proportion of controls using talc being similar across the two designs. The confidence intervals were overlapping suggesting that the findings were consistent. Recent updated meta-analysis discussed below report similar estimates from hospital and population based studies. (42). The RRs were relatively stable even after exclusion of the single cohort study or limiting the analysis to studies that controlled for body weight and BMI. The authors stated that the association between talc use and ovarian cancer could also be attributed to exposure misclassification among prevalent cases or side effects of treatment such as radiotherapy and chemotherapy which may predispose to talc use ("reverse causality"). Study limitations include the inability to conduct meaningful dose-response analysis because only nine of the 16 studies provided data on dose-response, with substantial differences in dose stratification levels among these studies.

5. Langseth reported on a meta-analysis of 20 case-control studies and one cohort study in 2008. The various case-control studies provided a significant excess risk (10 studies) and non-significant excess risk in 10 studies. (73). The prospective cohort study reported no association between cosmetic talc use and all types of ovarian cancer combined but showed evidence of an increase in serous tumors. The hospital-based case-control studies reported a pooled OR of 1.12 (95% CI: 0.92-1.36) and population-based case-controls studies reported a pooled OR of 1.40 (95% CI: 1.29-1.52). The combined OR from all case-control studies using the fixed effects model was 1.35 (95% CI: 1.26-1.46).

6. Terry et al conducted an individual participant pooled analysis of eight case-control studies was conducted by the investigators for the Ovarian Cancer Consortium. (10). Genital powder use was defined as any powder use (talc, cornstarch, deodorizing) applied directly or indirectly (with sanitary pads, tampons or underwear) to genital, perineal or rectal area. Criteria for exposure varied from ever use to one year or longer. Women who reported both genital and non-genital powder use were considered genital users. Cumulative exposure was calculated by multiplying months of use by frequency of use. Never users and women who reported non-genital powder use were considered as the reference group. Analyses were adjusted for potential confounders such as age, duration of contraceptive use, parity, tubal ligation history, BMI and race/ethnicity. Family history of breast and ovarian cancer was not included in the final model. Genital powder use was reported in 25% of controls and 31% of cases. The rates of genital powder use varied widely between studies ranging from 15-45% in the control group. Ever regular uses of genital powder reported a statistically significantly increased risk of ovarian cancer (OR 1.24, 95% CI: 1.15–1.33) compared to non-users. There was no evidence of heterogeneity in the studies regardless of the reference group ($P_{heterogeneity}$=0.61). Results were similar when the reference group included those with genital powder use and never users. Risk was elevated for various histologic subtypes of ovarian cancer including invasive serous (OR 1.20, 95% CI: 1.09–1.32), endometrioid (OR 1.22, 95% CI: 1.04–1.43), and clear cell (OR 1.24, 95% CI: 1.01–1.52) tumors, and for borderline serous tumors (OR 1.46, 95% CI: 1.24–1.72). There was an increased risk of all nonmucinous subtypes of epithelial ovarian cancer combined across quartiles of genital powder use compared with nonuse: (OR_{Q1} 1.18, 95% CI: 1.02–1.36; OR_{Q2} 1.22, 95% CI: 1.06–1.41; OR_{Q3} 1.22, 95% CI: 1.06–1.40; OR_{Q4} 1.37, 95% CI: 1.19–1.58). Although a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis (P_{trend} < 0.0001), no significant trend was seen when analyses were restricted to ever users (P=0.17). After excluding those with tubal ligation or hysterectomy, the results were similar. Restricting analysis to applications before tubal ligation made no substantive difference. There was an evidence of interaction by BMI, with the risk being higher for women with BMI < 30 kg/m^2 (OR 1.28, 95% CI: 1.17-1.39) than women with BMI ≥ 30 kg/m^2 (OR 1.14, 95% CI: 0.98-1.32; $P_{interaction}$=0.01). There was no evidence of interaction by tubal ligation, parity, endometriosis or post-menopausal status. The association was similar for women who used powder during varying time periods (1952-1961; 1962-1972; and after 1972). The strengths of this meta-analysis include the use of individual participant data, which allowed them to conduct dose-response analysis and analysis by histologic subtype. The lack of statistically significant evidence on non-

mucinous cancer could be attributed to the low number of users, or talc may not be relevant to these tumor types which have different biological mechanisms. The limitations include the definition of exposure as genital powder user varied from ever user, ever regular user to powder use for at least 6 months or at least 1 year in the studies.

7. Berge et al. 2018, a meta-analysis of 27 studies (41) (24 case-control studies and 3 cohort studies) was conducted according to the Preferred Item for Reporting of Systematic Reviews and Meta-Analysis Guidelines. (110). The authors searched multiple databases including Pubmed, Embase and Scopus. They examined the citations independently and in duplicate. They rated the studies using the New Castle Ottawa scale for study quality. They conducted meta-regression for duration (RR for every 10-year increase in duration) and frequency of genital talc use (RR for one time/week increase in frequency) for studies reporting at least three categories of duration or frequency after excluding the non-exposed category. Dose-response analysis was conducted using two methods. Study specific slopes were estimated from the natural logarithm of the risk estimates within each study; in a second step the slopes were pooled using a random-effects model. The study specific estimates were pooled in a single meta-analysis in the second method. Six of the case-control studies were hospital-based and the remainder were population-based. Most of the studies were conducted in North America and Europe. They reported a statistically significant increase in risk of developing ovarian cancer with talc use (adjusted RR 1.22, 95% CI: 1.13-1.30). A statistically significant risk was seen in the case-control studies (RR 1.26, 95% CI: 1.17-1.35), whereas the excess risk in the cohort studies did not reach statistical significance (RR 1.02, 95% CI: 0.85-1.20; $P_{heterogeneity} = 0.007$). There was no difference between results for borderline (RR 1.27, 95% CI: 1.09–1.44) and invasive ovarian cancer (RR 1.20; 95% CI: 1.08–1.31). There was a trend in RR with duration and frequency of genital talc use and suggestion of dose-response. There was a statistically significant risk for only serous carcinoma (RR 1.24, 95% CI: 1.15–1.34) and no other histologic subtypes ($P_{heterogeneity}$ between histologic types was 0.04). Use of talcum powder in the "early" period showed increased_risk of ovarian cancer (RR 1.18, 95% CI: 0.99–1.37). The use in the "late" period was higher (RR 1.31, 95% CI: 1.03–1.61; P-value for test for heterogeneity between the groups of studies was 0.37), arguing against the hypothesis that a higher risk would be seen only among those with earlier exposure during time-periods in which talcum powder was reported to contain asbestos. The cut-off points varied between studies was variable between 1970 and 1980. Use of sanitary napkins or diaphragms was not associated with an increased risk of ovarian cancer (RR 1.00: 95% CI: 0.84–1.16, and RR 0.75, 95% CI: 0.63–0.88, respectively).

Stratified analysis based on the adjustment for confounders (use of oral contraceptives and hormone replacement therapy, socioeconomic status/ education, BMI) found no evidence of heterogeneity. Meta-regression using the two different approaches yielded similar results. Based on the two-step approach, a 10-year increase in genital talc use was associated with a RR of 0.97 (95% CI: 0.82–1.12; nine studies reporting on duration), whereas the RR for an increase of one application per week was 1.03 (95% CI: 0.82–1.25; five studies reporting on frequency). There was no evidence of publication bias on visual inspection of funnel plot and the Egger test (P=0.7), with the cumulative meta-analysis reporting stabilization RR of in the range of 1.20–1.25. Stratified analyses conducted did not suggest the possibility of residual confounding (i.e, higher adjusted estimates than unadjusted estimates).

There are some limitations to the analysis. While the role of selection and recall bias is a possibility, given higher estimates reported from recent studies, such biases should account for increase in recall for all histologic cancer subtypes and not just serous ovarian cancer. Importantly, the dose-response analyses analyzed duration and frequency separately and not the intensity of exposure (duration combined with frequency) or cumulative exposure to talc and the exclusion of the reference category from the dose-response curve diminished the power of the dose response analysis to detect any threshold effects.

8. Penninkilampi, et al. 2018 (42), the most recent and comprehensive meta-analysis which focused on studies with greater than 50 cases of ovarian cancer also reported on data from 26 case-control studies (13,421 cases and 19,314 controls) and 3 cohort studies (890 cases). The study was also conducted according to the PRISMA protocol and included a search of multiple databases (MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials) and LILACS. They also evaluated the quality of studies using the Newcastle Ottawa Scale. They also evaluated long term talc use in which OR were extracted for group with the longest duration of exposure compared to controls, if there was a minimum of 10 years of talc exposure. Lifetime applications within each study were divided into < 3600 lifetime applications (equivalent to less than 10 years) and >3600 applications or more than 10 years of exposure. The number of lifetime applications is a better marker of intensity of exposure compared to duration or frequency of exposure alone. They assessed publication bias using the failsafe method where the failsafe number is the number of studies missed to nullify the findings of meta-analysis.

This was a well-conducted analysis and some strengths and limitations are notable. They found all studies to be of reasonable quality and did not exclude studies based on study quality. None of the analyses in this review had statistically significant heterogeneity except for non-perineal application arguing for the consistency of estimates. Any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, 95 % CI: 1.24-1.39). Greater than 3600 lifetime applications were more associated with ovarian cancer than lifetime applications of less than 3600, although risks were significantly elevated in both groups. While the case-control studies reported a statistically significantly increased risk of ovarian cancer (OR 1.35, 95% CI: 1.27-1.43), the cohort studies reported an increased risk which was not statistically significant (OR 1.06, 95 % CI: 0.90-1.25).

9. Meta-analysis on Talc-Dusted Diaphragms and Ovarian Cancer. Another meta-analysis of 9 case-control studies by Huncharek et al. (13) reported on exposure to talc dusted diaphragms and ovarian cancer. On one hand, the authors dismissed the "talc hypothesis" for potential carcinogenicity, but then argued that talc dusted diaphragms was a more "intuitive model" for testing whether talc exposure increased the risk of ovarian cancer without any biological evidence (or references) to support this intuition. They searched MEDLARS, Cancer Lit and Current Contents. They included 9 studies and the pooled analyses yielded an excess risk of ovarian cancer which was not statistically significant (RR 1.03, 95% CI: 0.80-1.33). Exclusion of the study in which exposure to dusted diaphragms was assumed rather than measured further elevated the OR, which was not statistically significant (OR 1.12, 95% CI: 0.84–1.48) similar to a non-significant elevation in OR after the exclusion of the studies not published as full research articles.

This meta-analysis was flawed for several reasons. The most important limitation was its exclusive focus on talc powder dusted diaphragms as the route of exposure which could not inherently address the causal question of whether genital talcum powder dusting is associated with increased risk of ovarian cancer. As a result of this narrow hypothesis, they excluded several available studies that reported a statistically significant excess risk of ovarian cancer with perineal talc use. Several methodological flaws include the exclusion of the lowest category of exposure for some studies, (51) data extractions errors for others (56), and inclusion of ineligible studies that did not disaggregate data between talc and cornstarch users. (77) The study was by Johnson & Johnson and Luzenac America and was of poorer methodological quality than those conducted by their academic counterparts (43). As a result of these serious methodological

flaws, and the publication of several newer, higher quality meta-analysis with updated data, (10, 41, 42) the findings of this study have been superseded.

It is important to note here that while the AMSTAR checklist evaluates the methodologic quality of systematic reviews, several studies shown below were published prior to the publication of the AMSTAR checklist.

IX.II. Case-Control Summaries.

1. More than three decades ago Cramer et al. (75) evaluated 215 white women diagnosed with epithelial ovarian cancer identified through 12 hospitals in the greater Boston area. They were randomly matched by age, race and residence to 215 population-based controls. Surgical specimens were reviewed to confirm and classify tumors by histologic type. Talc exposure was determined through in person interviews. Multivariable logistic regression was used to estimate the Relative Risk. Ninety-two (42.8%) cases regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls.

Adjusted for parity and menopausal status, this difference yielded a RR of 1.92 (95% CI: 1.27-2.89) for ovarian cancer associated with talc exposure. Women who had regularly engaged in both practices had an adjusted RR of 3.28 (95 % CI: 1.68-6.42; $P < 0.001$) compared to women with neither exposure. After adjusting for religion, marital status, educational levels, ponderal index, age at menarche, parity, oral contraceptive or menopausal hormone use and smoking the RR was attenuated but remained statistically significant (RR 1.61, 95% CI: 1.04-2.49). The limitations of the study include the potential for selection bias in controls because of high rates of non-participation, although RR remained statistically significantly elevated even though the analysis was restricted to 121 cases matched with controls without a referral. Since approximately 50% of ovarian cancer cases in the Boston area was sampled, any potential for pervasive selection bias of cases was minimal. Other potential limitations include the adjustment for only a limited set of confounders such as parity and menopausal status.

2. Hartge et al. 1983 (76) conducted a hospital-based case-control study of women with pathologically confirmed primary epithelial ovarian cancers matched to equal number of women for conditions other than gynecologic, psychiatric, or malignant diseases or pregnancy in the same hospitals in Washington, DC. Controls were frequency matched for age, race and hospital. Exposure to talc was ascertained through questions about reproductive and sexual history, medical history, drug use, and other exposures. The questions for talc use were added after the study began yielding 135 cases and 171 controls.

Among the women users of talc in sanitary napkins, underwear, or the genital area there was an excess risk of ovarian cancer (unadjusted RR 2.5, 95 % CI: 0.7-10.0) which was not statistically significant due to small sample size (n= 7 cases and 3 controls). The limitations to the study include the limited number of cases and controls reporting genital use of talc (n=10) and publication as a letter to the editor which may or may not undergo peer review depending on editorial practices at the journal. They did not report adjusted results of ovarian cancer after perineal exposure to talc. Another limitation is the potential for recall bias; however, this was likely minimal given similar reporting of douching practices in cases and controls.

3. In 1988, Whittemore et al. (58) evaluated 188 pre-menopausal and postmenopausal women between the ages of 18 and 74 with primary epithelial ovarian cancer in Santa Clara County hospitals or at the University of California, San Francisco Medical Center. The diagnoses were subsequently histologically verified. One group of controls was selected from the hospital (n=280); and a second group was selected from the population using random digit dialing (n=259). Exposure to talcum powder products was determined through a structured in-person interview at home where subjects were asked about whether they had used talcum powder products on the perineum, sanitary pads and/or diaphragms. Data was recorded by type (perineum, sanitary pads, diaphragm or some combination thereof), and duration of use.

Population cases were more likely to be younger and more likely to be premenopausal than cases and hospital-based controls. Approximately 52% of cases reported talc use compared to 46% controls (RR 1.40, p=0.6). After adjusting for parity and oral contraceptive use, perineal use of talc was associated with an excess risk of ovarian cancer that was not statistically significant (RR 1.45, 95% CI: 0.812.60). Women who used talc an average of 1-20 times per month reported an excess risk in comparison to those who used it less frequently which was not statistically significant (RR 1.27, p=0.29). The risk among users of more than 20 times per month was 1.45 times greater than non-users, but the findings were not statistically significant (p=0.09). The overall increased risk in overall applications per month was 1.30 (p=0.19). Although the data showed a *trend* of increasing risk with increasing frequency of perineal exposure, the trends were not statistically significant and there was no trend with increasing duration of exposure. The risk of ovarian cancer with talc use between one and nine years was 1.6 times the risk of those with a shorter duration (95% CI: 1.00-2.57; p=0.05), and the risk among those with more than 10 years of exposure was 1.11 higher than that of non-users (95% CI: 0.74-1.65; p=0.61).

The limitations of the study are the inability to interview cases and the choice of two controls. Some amount of non-differential misclassification of exposure may bias findings towards null. The dose-response analysis was limited by the inability to determine the combined effect of frequency and duration of exposure. The study reported a statistically increased risk of ovarian cancer with coffee consumption and a non-significant reduction in risk with smoking. Subsequent meta-analysis (111) or Mendelian randomization (112) studies have confirmed that there is no association between coffee consumption and ovarian cancer, whereas smoking has a heterogenous relationship to ovarian cancer which varies by histologic subtypes. (112) The reports of such additional spurious associations suggest an element of measurement error in their database.

4. Harlow et al. 1989 (77) conducted a population-based case-control study which included 116 females 20-79 years old h *serous and mucinous borderline ovarian tumors* identified using International Classification of Disease (ICD)-9 codes from the cancer registries of three western urban counties in Washington State. An independent pathology review confirmed diagnosis for 73% of tumors with 94% agreement, so the additional 33 cases were included. A sample of 158 controls of white women was identified through random digit dialing. Women with bilateral oophorectomy were excluded from the analysis. Any exposure to talc including any perineal exposure to powder, method of use, type of powder use (cornstarch, baby powder, talc, deodorizing powder), and combinations of method and type was ascertained through in-person interviews.

The study reported no statistically significant increased risk of ovarian cancer with perineal use of dusting powders (RR 1.1, 95% CI: 0.7-2.1). When looking at unspecified talc adjusted for the same factors, the RR was 1.0 (95% CI: 0.4-2.4). However, women who reported any use of talc containing powder on sanitary napkins showed an excess risk which was not statistically significant due to limited statistical power (RR 2.2, 95% CI: 0.8-19.8). However, among the sample of women who used deodorizing powders alone or in combination with talc, the risk of ovarian cancer was RR 2.8 (95% CI: 1.1-11.7) attributed to the potential exposure to asbestos. The limitations to the study include the potential for selection bias since 30% of cases and controls did not participate, although their characteristics were like the included participants which may have limited any impact. It is also possible that these findings are limited to borderline rather than malignant ovarian cancers.

5. In 1989, Booth et al. (51) conducted a population-based case-control study of 280 cases of ovarian cancer in women under 65 years of age from 13 hospitals in London and two in

Oxford. 451 controls were selected from other hospitals as enough age-matched controls were unavailable. The study included both pre- and post-menopausal women. Ovarian cancer was determined through hospital diagnoses with pathological specimens being histologically classified. Serous tumors were most prevalent, though mucinous, endometroid and clear cell carcinoma was included. Information regarding talc exposure was obtained through a questionnaire and frequency of talc use was reported as never, rarely, monthly, weekly, or daily talc use.

After adjusting for age and social class (based on occupation of the husband for married women, and their own occupation for women who were not married) talc users reporting use more than once a week had a higher risk compared to never users. (RR 2.0, 95 % CI: 1.3-3.4). Those who reported daily use also had a non-significantly higher risk (RR 1.3, 95% CI: 0.8-1.9). There was some amount of missing data (8% of cases and 4% of controls), and no consistent trend of increasing risk with increasing frequency of use. However, data was not available on the duration of talc exposure to conduct meaningful dose-response analysis.

6. In 1992, Harlow et al. (79) included 235 cases of white women between the ages of 18 and 76 who had been diagnosed with ovarian cancer at one of 10 hospitals in the Boston metropolitan area. Controls were randomly selected from the town books; annual publication lists and address lists within 2 years of the age of case as potential controls. Cancer was confirmed through an independent pathology review. Talc exposure was determined through in-person interviews. Talc exposure from infancy with diapering, or use on other parts of the body, was not included. Talc use in other parts of body was considered unexposed. Talc use was reported as any genital application, type of application (sanitary napkin/underwear, via partner or application to diaphragm, via dusting to perineum), number of applications per month, years of use, age at first use, years since last use, whether use was before or after 1960, brand of application, estimated total lifetime applications, estimated applications excluding use after hysterectomy or tubal ligation, and estimated applications excluding use after hysterectomy or tubal ligation and use during nonovulatory months. The Chi square test for change in linear trend based on change in deviance in models.

Most participants reported use of baby powder. Perineal talc use was associated with an increased risk for ovarian cancer (OR 1.5, 95% CI: 1.0-2.1) when adjusted for parity, education, marital status, religion, use of sanitary napkins, douching, age, and weight. Perineal use of talc via dusting powder to perineum was associated with a significantly increased risk of ovarian cancer OR 1.7 (95% CI: 1.1-2.7), whereas use by sanitary napkins, underwear, use via

diaphragms was not associated with a significantly increased risk. Adjusted risk was highest for endometrioid tumors (OR 2.8, 95% CI: 1.2-6.4) and borderline tumors. A greater proportion of women with endometroid tumors reported more than 10,000 lifetime applications of talc during ovulatory cycles while having an intact genital tract compared to other histologic types (34 % vs 16%, respectively). The risk of cancer increased significantly with increased frequency of applications per month using a linear test trend as a continuous variable. The risk was highest among the women who applied talc once daily relative to non-users. Women who applied talc for more than 10 years were at 60% greater risk for ovarian cancer relative to non-users. An 80% excess risk was associated with an estimated exposure of more than 10,000 applications. The association between talc and ovarian cancer was greater than in talc products before 1960. Restricting the analysis to exposure during ovulatory months, women with intact genital tract and more than 10,000 applications during ovulatory cycles had a threefold increase in risk of ovarian cancer. Limitations included the high rates of non-response (n=31% cases and 19% of controls) and failure to adjust for family history of ovarian cancer and oral contraceptive use.

7. Chen et al. 1992 (78) evaluated 112 cases of ovarian cancer in Beijing China. The diagnosis was confirmed by laparotomy and pathological examination. Serous cancer accounted for 51% of cases, mucinous for 19%, and miscellaneous epithelial for 30% of cases. Two controls were matched for each case using random selection from the same street, office, or township. A comprehensive questionnaire was administered through face-to-face interviews and collected information about menstrual, obstetric, marital, medical, familial, and dietary histories with reference to events 3 years or more prior to diagnosis. A total of 224 controls were selected. Talc exposure was measured through a yes or no metric, for exposure occurring 3 or years prior to date of diagnosis or equivalent date in controls. Logistic regression was conducted to estimate relative risk.

The mean age of participants was 48.5 and 49 years among cases and controls respectively. After adjusting for education and parity, there was an excess risk of ovarian cancer associated with a history of long-term (>3 months) application of dusting powder to the lower abdomen and perineum (RR 3.9, 95% CI: 0.9-10.6) which was not statistically significant due to limited statistical power (n=7 cases and 5 controls reporting powder use). The limitations of the study include the small sample size, loss to follow up and death, the inability to fully ascertain all cases of ovarian cancer and the exclusion of controls with other health problems. Although the applicability of these findings from a Chinese population to a US population is limited, the

findings of an increased risk in different parts of the world provide evidence in support of an increased risk of ovarian cancer with dusting powder use.

8. In 1992 Rosenblatt et al. (80) conducted a hospital-based case-control study of the association between genital and respiratory talc exposure and the development of epithelial ovarian cancer at the Johns Hopkins Hospital. Among 140 diagnosed cases of epithelial ovarian cancer, approximately 108 were successfully interviewed. Seventy-seven pathologically-confirmed incident cases diagnosed within 6 months of admission were matched to age-race matched controls (n=46). Exposure was ascertained using a structured questionnaire administered at home and in the hospital. Conditional logistic regression was used to obtain strength of the association.

Although genital powder use was not associated with an increased risk of ovarian cancer, statistically significant increased risk was observed for exposure to talc on sanitary napkins (OR 4.79, 95% CI: 1.29-17.79) after adjusting for confounders such as obesity, socioeconomic status, religion, reproductive status and oral contraceptive use, with a smaller risk after genital bath exposure (RR 1.7, 95% CI: 0.7-3.9). An excess risk of borderline significance was seen for exposure of ≥ 37.4 years (RR 2.4, 95% CI: 1.0-5.8). The limitations include the small sample size, lack of data on frequency of talc use, and the limited generalizability of the findings from one hospital. The control group also reported a very high rate of talc use (90%) which may have limited the ability to detect any differences.

9. In 1993, Tzonou et al. (81) reported on a hospital-based study of 189 women under 75 years of age with histopathologically confirmed ovarian cancer in Athens, Greece compared with 200 hospital visitor controls in two hospitals. Control patients were those hospitalized in the same ward as cancer cases. Talc exposure was determined by asking participants to report talc use (over an extended period before the onset of illness for cases and for a comparable period among controls) among other characteristics, through interviews in the hospital. Talc use was reported as a yes/no metric. Estimates were adjusted for age, years of schooling, weight before onset of the disease, age at menarche, menopausal status and age at menopause, parity and age at first birth, tobacco smoking, coffee drinking, consumption of alcoholic beverages, hair dyeing and mutual (analgesics-tranquilizers/hypnotics) tranquilizers.

An exceedingly small number of cases (n=6) and controls (n=7) reported perineal use of a talc. There was no statistically significant increased risk of ovarian cancer associated with perineal application of talc (RR 1.05; 95% CI: 0.28 to 3.98). The limitations of the study include the low

proportion of talc exposure, which was ascertained in only approximately 3% of cases and controls.

10. In 1995, Purdie et al. (82) evaluated 824 histologically confirmed cases of epithelial ovarian cancer and 860 controls from gynecological oncology treatment centers in the three most populous Australian states. Controls were selected from electoral rolls in Australia where electoral participation is mandatory using a random procedure to match the age distribution of cases. Talc exposure was determined through face-to-face interviews conducted by trained interviewers using a standard questionnaire.

After adjusting for parity, there was a statistically significant increase risk of ovarian cancer reported with talc use on the abdomen or perineum (OR 1.27, 95% CI: 1.04-1.54). The limitations include high non-response rates in controls which may differ from the source population, but the age distribution of controls was like non-responders suggesting minimal response bias by age. There is also the possibility of bias in the selection of cases. They only adjusted for a limited set of confounders. Some misclassification of outcome is also possible given borderline and malignant cases were lumped together, although no differences were found when results were analyzed separately. Recall and interviewer bias was minimized by trained interviewers who administered standardized questionnaires.

11. In 1996 Shushan et al. (83) reported on findings from a study of two hundred living cases aged 36-64 years with history confirmed diagnosis of primary invasive or borderline invasive ovarian cancer in the Israel Cancer registry. There were 408 women from the same area selected by random digit dialing. Both were interviewed using standardized questionnaires.

A larger proportion of cases than controls reported using moderate to a large amount of talc (10.5% vs 5.6%; P=0.04) compared to never users or seldom users, a difference which was statistically significant. Limitations include high refusal rate for cases (30%), the low rates of talc exposure among controls and limited adjustment for confounders. (14)

12. In 1997, Cook et al. (84) reported on 329 white women between the ages of 20-79 diagnosed with epithelial and borderline ovarian cancer identified through the Cancer Surveillance System of Western Washington. Women were randomly selected as controls using random digit dialing from a larger pool of women for cancer studies. Genital powder exposure was collected through structured in person interviews and reported as any lifetime powder application, method of use (perineal dusting only, diaphragm only, sanitary napkin only, or genital deodorant spray only). Additional exposure information included cumulative

lifetime days of use for dusting and similar metrics for other methods of use. Genital powder use was also separated into use of talcum powder, baby powder, cornstarch, deodorizing powder, bath/body powder, or unspecified powder. Analysis was presented by age because adjustment for other confounders such as income, marital status, body mass index, oral contraceptive or parity did not change results.

Genital powder exposure was more common among cases (50.8%) than controls (39.3%). After adjusting for age, any use of genital powder was associated with a statistically significant increased of ovarian cancer (RR 1.5, 95% CI: 1.1-2.0) compared to non-use, although there was no clear pattern of increasing risk after increasing duration of use. After adjusting for age, exclusive use of perineal dusting was also associated with a statistically significant increased risk of ovarian cancer (RR 1.8, 95% CI: 1.2-2.9), whereas the risks for use via other routes of exposure (e.g. diaphragms, powder) were not significant. There was a statistically significant increased risk of serous tumors associated with any genital powder application (RR 1.7, 95% CI: 1.1-2.5), but not for the smaller number of mucinous or endometroid tumors. Limitations include low participation rates (64.3% for cases, 68% for controls), the potential for recall bias, and confounding by family history of ovarian cancer in a study where more than 50% of controls were less than 45 years of age.

13. In 1997, Chang et al. (56) conducted a population-based case study of cases of borderline and invasive histologically confirmed ovarian cancer among participants aged 35 to 79 years from Canada. Talc exposure was determined through a questionnaire conducted during an in-home in person interview to detail medical and reproductive histories. Powder use was reported as talc, cornstarch, or a mixture. Information was provided for type of exposure, number of uses per month, years of use, years of use pre- and post-1970, and well as years of use before and after a tubal ligation or hysterectomy. They adjusted for age, years of oral contraceptive use, number of full-term pregnancies, duration of breastfeeding per pregnancy, tubal ligation, hysterectomy, and having a mother or sister with breast or ovarian cancer.

Talc exposure was reported in 44% of cases and 35.6% of controls. After adjusting for confounders there was a statistically significantly increased risk of ovarian cancer associated any talc exposure via sanitary napkins, direct application to the perineum or both (OR 1.42, 95% CI: 1.08-1.86). The dose-response analysis showed a borderline-significant association was detected between duration of after-bath talc exposure and risk (OR 1.09, 95% CI: 0.98-1.21, per 10 years of exposure), without any significant association between frequency of exposure and

risk. Although risk was elevated for both invasive and borderline carcinomas, it was statistically significant only for invasive carcinoma. The limitations of the study include the potential for recall bias and the high rates of non-response (28.7% for cases and 35.5% for controls)

14. Green et al. 1997 (62) conducted a population based case-control study of 824 women aged 18-79 with histologically confirmed ovarian cancer compared to 824 controls. The methods and limitations were similar to the study by Purdie et al. (82). The prevalence of talc use was approximately 40% in the control use. Perineal talc was significantly associated with ovarian cancer (RR 1.3, 95% CI: 1.1-1.6), without any effect of longer duration of talc use. Compared to women who had neither used talc nor had sterilization, the risk was highest among talc users without surgery like the findings by Whittemore et al. (58). There is the potential for recall bias, and the quantity of talc use was unknown.

15. In 1998, Godard et al. (85) examined 170 French-Canadian women with a histologic diagnosis of ovarian cancer from 2 large Montreal teaching hospitals. Cancer diagnoses were histologically confirmed, and pathology reports were reviewed for tumor classification. 170 population-based controls were identified using modified random digit dialing to match the age distribution of cases. Talc exposure was obtained through a 57-item questionnaire. 70% of interviews were conducted in person in clinics and 30% were conducted via phone. Talc use was reported through an ever/never metric for perineal use.

Only 10.6% of cases and 4.7% of controls reported talc use. As a result, perineal talc use was associated with an increased risk for ovarian cancer which was not statistically significant (RR 2.49, 95% CI: 0.94-6.58; P = .066) because of limited statistical power. Similar patterns of excess risk which did not reach statistical significance were seen in both the comparisons for sporadic and familial cases and controls. The limitations of the study include a modest non-response rates among cases (13%) and controls (10.7%).

16. In 1999, Cramer et al. (57) evaluated 563 ovarian cases identified through tumor boards and statewide cancer registries in Massachusetts or New Hampshire in a population-based control study. Pathology reports were reviewed, and slides were sought in any case where there was a discrepancy between histologic description and final diagnosis. Controls were selected from the population using random digit dialing with a response rate of 72% among eligible controls. Talc exposure was obtained through questionnaires in which potential controls and cases were blinded. Specific hypothesis regarding talc use were not discussed. Exposure was assessed prior to 1 year before date of diagnosis or date of interview for

controls. Talc use in the genital or rectal area, on sanitary napkins and on underwear was considered as exposure whereas non-use and non-genital use was considered as unexposed. Exposure from condoms and diaphragms was not assessed.

Genital talc exposure was reported in 27% of cases and 18.2% of controls and the average duration of talc use exceeded more than 20 years in cases and controls. There was a statistically significantly increased relative risk of ovarian cancer with genital talc exposure 1.60 (95% CI: 1.18-2.15) after adjusting for age, study center, tubal ligation, BMI, parity, or primary relative with breast or ovarian cancer. The highest risk was seen among women whose age at first use was between 20 and 25 (RR 1.87, 95% CI: 1.03-3.39) those who have used talc for less than 20 years (RR 1.86, 95% CI: 1.16-3.00), those whose total applications is less than 3000 (1.84, 95% CI: 1.12-3.03), women who used talc when nulliparous (RR 2.80, 95% CI: 0.64-12.20), and those with serous invasive tumors (RR 1.70, 95% CI: 1.22-2.39). Only one case and 3 controls reported primarily using cornstarch, these numbers are likely accurate for talc use, despite the potential for including other kinds of powders. There was little evidence of effect by confounders such as age, oral contraceptive use and parity. Linear trends were significant in models that included women who were not exposed without any clear trend in duration or intensity of exposure in models that excluded women who were not exposed. Analysis of dose-response censured after closure of female tract or non-ovulatory cycles, and models showed a trend this was statistically significant only after inclusion of non-genitally exposed categories (P_{trend}=0.022).

Potential limitations include the potential for recall bias, although this is likely to be minimal and more likely to occur for short term exposures rather than long term exposures. The evidence for substantial degree of recall bias is refuted by the findings that there is no evidence of higher proportion of perineal talc exposure reported among cases in more recent compared to older studies to suggest stimulated reporting, no evidence of significant excess of non-genital talc exposure among cases, and the excess is limited to invasive serous carcinoma,(84) rather than all types of ovarian cancer or endometrial carcinoma.

17. In 1999, Wong et al. (86) reported-on a hospital-based study of 499 patients with epithelial ovarian cancer and 775 age-matched controls with non-gynecologic cancer diagnoses. Cancer diagnoses were confirmed in the cancer registry. Exposure was ascertained through self-administered questionnaire in which approximately 15% of participants did not respond to questions about talc use or its frequency.

Talc use was reported by 47.8% of cases and 44.9% of controls. Genital talc use was reported by 34% of cases and 32.2% of cases. The mean duration of talc use was 22 years in controls and 21 years in the study population. After adjusting for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy there was no statistically significant increased risk of ovarian cancer among ever users of talc (OR 0.92, 95% CI: 0.24-3.62). There was no significant association between duration of use and development of ovarian cancer even after prolonged exposure of more than 20 years. However, when evaluating genital talc use via histologic subtypes of cancer, all ORs were above 1 (except for undifferentiated carcinoma) but were not statistically significant. Similarly, those who had no history of genital tract interruption the ORs were elevated but not statistically significant. However, the study was limited by the non-response rate and the choice of a controls with malignancies. (113). Additionally, data on exposure were reported on a self-administered questionnaire rather than administered by interviewers. The results could not rule out the effect of talc exposure via condom use and data was not available on the frequency of talc use.

18. Ness et al. (87) conducted a population-based control study. Cases (20-69) years of age with recent diagnosis of ovarian cancer (n=) were compared with community-based controls 65 years or younger through random digit dialing. Controls were age-matched as well as matched by last 3 digits of the phone number. Approximately 72% of controls were selected. As a part of detailed interviews with calendars women were asked about their reproductive history including talc use. The question was, "As an adult and prior to [reference date] did you ever use talc, baby or deodorizing powder, at least once per month for 6 or more months on your: 1) feet, arms, or breasts, but not the genital or rectal areas? 2) genital or rectal area? 3) on your sanitary napkins? 4) on your underwear? 5) on your diaphragm or cervical cap?" They were then asked whether they had a male sexual partner(s) for more than a year who regularly used such products on his genital area or underwear. The duration of use of talc for each of these modes of use was also queried. The estimates were analyzed using conditional logistic regression after adjusting for age and gravidity (each as continuous variables), race (white/black/other), history of ovarian cancer in any first degree relative (yes/no), oral contraceptive use (yes/no), tubal ligation (yes/no), hysterectomy (yes/no), and breast-feeding (yes/no).

Talc use was reported in 53.2 % of controls. Compared to never talc use, talc use on all parts of the body (OR 1.4, 95% CI 1.1-1.6), genital/rectal (OR 1.5, 95% CI 1.1-2.0) on sanitary napkins

OR 1.6, 95% CI 0 1.1- 2.3) and underwear OR 1.7, 95% CI. 1.2-2.4) was associated with a statistically significantly increased risk of ovarian cancer after adjusting for confounders. However, talc use on diaphragms (OR 0.6, 95% CI 0.3-1.2) or by male partner (OR 1.0, 95% CI 0.7 to 1.4) was associated with an increased risk which was not statistically significant. Although duration of talc use did not show a pattern of increased risk with increased risk with duration of exposure, the OR for each categories (> 1 year, 1-4 years, 5- 9 years and > 10 years) were elevated and were statistically significant for 1-4 years. Tubal ligation and hysterectomy decreased ovarian cancer risk. Limitations to the study include the low response rates among cases and controls due to exclusion of prevalent ovarian cancer. Recall bias while always a concern was less likely to be a concern given that risk factors overall did not increase risk but were limited to those linked to inflammation.

19. In 2004, Mills et al. (59) conducted a population-based case-control study of 256 women with histologically confirmed incident epithelial ovarian cancer from 22 counties in Central California. They also selected 1122 controls who were residents of that area who had one intact ovary and no history of ovarian cancer. Talc exposure was determined through phone interviews conducted by trained interviewers. Talcum powder use in the genial area was reported as an ever/never metric, as well as by frequency, duration, and cumulative use. The final parsimonious model adjusted for age, race, duration of oral contraceptive use and breast feeding.

The rates of talc use in controls was 37.1 % and higher among white non-Hispanics. Controls were more likely to have been outside the US. Most of talc exposed cases and controls were non-white. There was a statistically significant risk of ovarian cancer associated with genital talcum powder use (OR 1.37, 95% CI: 1.02-1.85) after adjusting or age, race, duration of oral contraceptive use, and breast feeding. Although increasing frequency of use showed a 74% increased risk among women who used talcum powder more than 4-7 times per week (P_{trend}= 0.015), this risk was not monotonic because risk the decreased between second (rarely to several times per month) and third categories (1 to 3 times per week). Duration of use also showed increasing risk and peaking between 4-12 years of use and declining thereafter (P_{trend} =0.045). Cumulative exposure increased in the second and third quartiles of exposure but declined among the highest quartile of users (P_{trend}=0.051). The risk was highest among those who had stopped using talcum powder in the last 1-2 years compared to those in the more distant past. The risks were primarily elevated for serous and mucinous tumors. Risk was higher among those reporting use after 1975 which may be related to the recency of use, and those after age 20. Limitations of the study include a low response fraction which was only

40% for eligible cases and 57% for eligible cases, and high rates of non-participation- 34.2% among cases and 29.3% among controls. The dose-response analysis did not exclude exposure during non-ovulatory periods or after gynecologic surgery which may have diluted the relative risk estimates. However, strengths include the ability to rule out prevalent cases by examining incident cases alone.

20. In 2004, Langseth et al. (88) conducted a case-control study of pulp and paper workers from different mills in Norway. Only one of these mills reported use of fibrous talc. They included 46 cases and reviewed histological records for each case. Most of the cases were invasive tumors. Four controls free of ovarian cancer and having intact ovaries were matched by birth year +/- 2 years and were drawn by incidence density sampling. A total 179 controls were available for analysis. Talc exposure was determined through personal interviews which took place in mill offices, at home, at a medical institution, or by phone. Talc exposure was reported environmentally and as use by personal hygiene (diapers, sanitary napkins, non-genital area or husbands use in genital area)

Talc exposure was reported among 50% of cases and 48% of controls. After adjusting for number of children, breastfeeding, age at birth of first and last child, age at menarche, age at menopause, smoking, and family history the use of talc use by personal hygiene was associated with an excess risk of ovarian cancer OR 1.15 (95% CI: 0.41-3.21), which was not statistically significant. The study has significant limitations. The sample size of the study was low with limited statistical power to detect a two-fold increased risk with a probability of only 53 % and response rate for interviews were low -76.1% for cases and 65.7% for controls. The inclusions of non-genital or husband's use in genital area among the exposed category diluted the estimates of relative risk for ovarian cancer associated with talc exposure. More information on cases was collected from relatives than controls because 71.5 of cases were deceased compared to only 28.6% of controls. The rates of missing data on talc use was high, because it was obtained from proxy respondents introducing an element of uncertainty in the estimates for relative risk of ovarian cancer associated with talc use.

21. In 2008, Merritt et al. (89) reported on a population-based study of 1,576 women with epithelial ovarian cancer as part of the Australian Ovarian Cancer Study. Pathology reports and diagnostic slides were reviewed for a sample of 87 women with 97% agreement with original abstracted data. Cases were confirmed by histopathology. 1509 controls were selected from the electoral rolls and were matched by age and residence. Talc exposure was identified through a comprehensive health and lifestyle questionnaire. Talc use was reported as

ever/never for perineal use (powder or talc in the genital area or on underwear or on sanitary napkins), years of use prior to surgery, use post-surgery, and use stratified by age at diagnosis. All analyses were conducted for talc use while the reproductive tract was patent and exposure occurring 12 months prior to the diagnosis of cases and similar period in controls was excluded.

The rate of talc use was 43% among controls and 46% among cases. When adjusted for age, education, parity, and oral contraceptive use of talc in the perineal region among women with patent tubes there was a statistically increased risk of ovarian cancer (OR 1.17, 95% CI: 1.01-1.36) with the highest risk reported for serous tumors (OR 1.21, 95% CI: 1.03-1.44). The tests for trends for duration of use were of borderline statistical significance for all cancers and serous subgroup (P_{trend} =0.02 for both). No significant associations between number of years used pre- or post-surgery and significantly elevated risks for overall cancer and serous ovarian cancer were seen in women both above 70 years of age, and below 50 years of age suggesting that timing of talc exposure (before or after 1976) did not affect results. There was no association between PID and the risk of ovarian cancer or the protective effect of NSAIDs. Limitations include low response rates and the lack of data on the frequency of exposure.

22. In 2008 Gates et al. (55) conducted a nested case-control study as part of the New England Case-Control study and the Nurses' Health Study (NHS). Further cohort analysis from the NHS are presented in the section on cohort studies below. **Section IX.III.I** Ovarian cancer diagnoses were confirmed by the researchers. They included 1385 cases and 1802 controls. 76.7 % of cases were incident with respect to the timing of DNA collection in the NHS. Exposure was accessed through a questionnaire that asked questions related to use of talcum powder. The NECC questionnaires included questions about regular use of talcum, baby or deodorizing powder as an adult. Specific questions asked about type of use (as a dusting powder to the genital area, sanitary napkins, underwear, or non-genital areas), frequency of use, age at first use, number of years used, and brand of powder used. The 1982 NHS questionnaire requested information on whether the participant had ever commonly applied talcum, baby, or deodorizing powder to the perineal area (no, <once/week, 1-6 times/week, or daily) or to sanitary napkins (yes/no). The study defined regular genital talc use as application of powder to the genital/perineal region at least once per week. We also created a categorical variable for frequency of talc use, using the categories from the NHS questionnaire.

Most of the participants were white. Regular genital talc was reported among 56 cases and 44 controls, and daily genital talc use reported among 35 cases and 25 controls, respectively. There was a statistically significant increased risk of total epithelial ovarian cancer (RR 1.36, 95% CI: 1.14-1.63; P<0.001) and of serous invasive subtype (RR 1.60, 95% CI: 1.26-2.02) associated with regular use of talc when adjusted for age, study center, duration of oral contraceptive use, parity, tubal ligation, BMI, and duration of hormone use. The New England Case-control study had a higher RR associated with genital talc use than the Nurses' Health which had a smaller sample size. There was a statistically significant trend between increasing frequency of talc use and risk of both total and serous invasive ovarian cancer in the pooled analyses (P *trend* < 0.001 for both total and serous invasive ovarian cancer). The association between talc and ovarian cancer was stronger among women with the glutathione S-transferase M1 (GSTM1) null genotype (P interaction = 0.03), particularly in combination with the GSTM1 present genotype alone (P interaction = 0.03) in two independent study populations. The strengths of the study include robust findings from two independent study populations. Although talc exposure was only measured in the 1982 NHS questionnaire when participants were between 36 to 61 years of age, the number of users who began talc use after this is likely small as shown by the fact that more than 95% of controls with regular talc in the NECC reported talc use before age 35. The consistent findings from the prospective NHS study and the NECC may have minimized any potential biases due to the case-control design. Since talc exposure was defined as at least once per week, such habitual exposure is less susceptible to recall bias than sporadic exposure.

23. In 2009, Wu et al. (48) conducted a population-based study of 609 cases of women and 688 controls between the ages of 18 and 74 residing in Los Angeles with histologically confirmed incident invasive or borderline ovarian cancers. Cases were identified through the Surveillance, Epidemiology and End Results (SEER) Program. Cases were matched to neighborhood controls on age and race/ethnicity. Controls were women with one intact ovary with no history of cancer except non-melanomatous skin cancer matched on age and race/ethnicity. Talc exposure was determined through a detailed interview by the same person which included a comprehensive questionnaire that used a reference date of 2 years before the date of diagnosis (or date of interview for controls). Talc use was reported as a yes or no metric (including yes or no for perineal area use), frequency and duration, total times of use, and total times of use before and after 1975. Few users of talc (24) had tubal ligation or hysterectomy prior to talc use and were considered as non-users.

The cases were primarily white woman but also included 41 African American women, 136 Hispanic women, and 51 Asian women. After adjusting for race, age, education, tubal ligation, family history, menopausal status, use of oral contraceptives, and parity perineal use of talc was associated with a statistically significantly increased risk of ovarian cancer (RR 1.53, 95% CI: 1.13-2.09). Elevated risks were also noted among those who used it on sanitary napkins, underwear and on diaphragms but not significant due to limited statistical power. There was a clear trend of increasing risk with increasing frequency of use among users who had used it for more than 20 years. The risk of ovarian cancer increased significantly with increasing frequency and duration of talc use; compared to never users, risk was highest among long duration (20 years), frequent (at least daily) talc users (RR 2.08, 95% CI: 1.34-3.23). The risk increased significantly with lifetime total times of talc use, but the association was limited to those who started talc use before 1975 (P_{trend} <0.001). The association between talc use and ovarian cancer was strongest for serous ovarian cancer. Risk of ovarian cancer increased with the diagnosis of endometriosis. Limitations include the rates of non-response among cases and controls, and classification of talc use among a small number of users with prior hysterectomy as being non-exposed. However, the effect of this misclassification is likely to be minimal.

24. In 2009, Moorman et al. (90) reported on a study involving 1,114 cases with histopathologically confirmed tumors as part of the North Carolina Ovarian Cancer Study. newly diagnosed cases were identified through the North Carolina Central Cancer Registry. All cases were confirmed by histopathologic review. Controls were frequency matched to cases and recruited from the same geographic region using random digit dialing. The controls could not have had a bilateral oophorectomy. Talc exposure was reported through in-person interviews conducted by nurses with life calendar and pictures of contraceptives, menopausal hormones, and other medications were used to help aid recall. Talc use was reported as a yes/no metric.

The analysis focused on invasive ovarian cancer which comprised of 78% of cancers for African-Americans and 79% for whites. Among controls, talc use was reported by 23.9% among whites and 31.2% of African-Americans. After adjusting for age there was an excess risk reported for both whites (OR 1.04, 95% CI: 0.82-1.33) and African Americans (RR 1.19, 95 % CI: 0.68-2.09) which were not statistically significant. Limitations include the high rates of non-response (33.5% among cases, 39.1% among controls), with higher non-response rates among African-Americans. There was a large proportion of missing data on talc use for cases and controls; 23.6% and 38.5% among whites, respectively, and 25.2% and 29.1% among African Americans, respectively, resulting in misclassification of exposure. The authors did not

clarify the route of talc exposure and may have classified non-genital talc exposure to the talc exposed group which may have diluted the RR. Additionally, the study did not adjust for confounders to address the timing, frequency and duration of talc exposure, or whether talc exposure occurred before or after tubal ligation or hysterectomy.

25. In 2011, Rosenblatt et al. (60) reported on a study of women between the ages of 35 and 74 from 13 counties in Washington state. Cases of borderline or invasive epithelial ovarian cancer were identified through the Cancer Surveillance System. Controls were selected from the population using digit dialing. Talc exposure was determined through in person interviews which included a reference period of unstated length before diagnosis or interview. For powder use on sanitary napkins and deodorant spray, the total number of months of use was recorded. For powder use on perineum after bathing, only intervals of at least one year when powder was usually used was recorded. Talc use was reported as genital powder exposure by type of use, duration of use, lifetime applications, age at first use, age at last use, calendar year of first use, time since first use, and time since last use.

Perineal use of powder after bathing was reported in 12% of controls. Reporting of cornstarch was uncommon in the study. After adjusting for age, calendar year of diagnosis, county of residence, number of full term live births, and duration of hormonal contraception the perineal use of powder after bathing was associated with an increased ovarian cancer risk (OR 1.27, 95% CI: 0.97-1.66) which was not statistically significant, but a statistically significant increased risk was seen among women with borderline tumors (OR 1.55, 95% CI: 1.02-2.37), similar to that reported by Harlow et al. (79) There were no differences in risk among various types of powder use, as the risk among those who reported use of talcum powder was RR 1.38 (95% CI: 0.77-2.47). There was no difference in exposure outcome relationship between talc use before and after 1980. There was no pattern of risk associated with perineal dusting powder and the increasing extant of use as defined by years in which it was used or number of lifetime applications. The participation rate of cases and controls was modest at 76.8% and 69%. Some misclassification of exposure is possible as participants may be unable to provide accurate information on whether the specific powder contained talc. However, the presence of talc, rather than a specific dose, is the primary determinant of exposure in which case genital powder use is a reasonable proxy for talc exposure.

26. Kurta et al. 2012 (91) reported on a case-control study from the Hormones and Ovarian Cancer Project using 902 ovarian cancer cases and 1802 controls. Participants were diagnosed with histologically confirmed ovarian, fallopian tube or peritoneal cancers. They were at least

9 years old and within 9 months of diagnosis. Controls were frequency matched by age and area code to cases at 2:1 ratio. Trained interviewers collected data via questionnaires. Perineal talc use was defined as ever using dusting powder or deodorizing spray on the genital or rectal areas, on sanitary napkins or underwear or on diaphragms or cervical caps.

Perineal talc use was reported among 20.9% of controls and 27.6% of cases. After adjusting for age, race, education perineal talc was associated with a statistically significantly increased risk of ovarian cancer OR 1.40 (95% CI: 1.16-1.69). Limitations include the population which was women seeking treatment for infertility which may limit generalizability.

27. In 2015, Wu et al. (53) evaluated 1,701 newly diagnosed histologically confirmed cases of invasive epithelial ovarian cancer cases of ovarian cancer among participants aged 18 and 74 in Los Angeles county identified through the USC Cancer Surveillance Program. Cases were primarily white but 308 Hispanic Women and 128 African American women were also included. Controls were selected from residents of LA county and were matched to cases on race/ethnicity and year of birth. Talc exposure was ascertained through in person interviews conducted using standardized questionnaires with a reference date of 12 months prior to diagnosis (or date of interview for controls). Genital talc was reported as no use or less than one year of use, yes use, and use per 5 years of talc.

Among controls the prevalence of talc use ≥ 1 year was 30.4% in non-Hispanic whites, 28.9% in Hispanics and 44.1%. After adjusting for several confounders including race, age group, menopausal status, age at menarche, hormone therapy use, BMI, income, education, life births, tubal ligation, oral contraception, endometriosis, and first-degree family history of ovarian cancer there was a statistically significant increased risk of ovarian cancer associated with genital talc use across all races (OR 1.46, 95% CI: 1.27-1.69), non-Hispanic whites (OR 1.41, 95% CI: 1.21-1.67), and Hispanics (OR 1.77, 95% CI: 1.20-2.62) compared to non-use or less than 1 year of use. The risk was elevated but not statistically significant among African-Americans (OR 1.56, 95% CI: 0.80-3.04) because of low statistical power for the subgroup. Every 5-year use of talc was associated with a statistically significant risk of cancer among the overall population (OR 1.14, 95% CI: 1.09-1.20) and non-Hispanic whites and Hispanics, whereas the excess risk among African-Americans was not statistically significant. The non-response rate for cases (36.8%) and controls was modest. There was no evidence of systematic bias in the ascertainment of exposure as prevalence of various conditions such as endometriosis was consistent with other prior studies.

28. Schildkraut et al. 2016 (52) evaluated African women aged 20-79 years of as part of the African-American Cancer Epidemiology Study. They selected 584 cases of newly diagnosed epithelial ovarian cancer and matched 745 controls to cases on age and region of residence using random digit dialing. Talc exposure was determined through a telephonic interview which included information on baby powder use. Participants were considered regular users if they reported use at least more than 1 time per month for 6 months. Regular users were asked about genital or nongenital use, frequency, duration, and lifetime applications (number of applications per month by number of months used). Since there was a small number of users who reported only genital powder use, they were grouped with genital and non-genital users to "any" genital use. Exposure was examined by frequency of use (less than 30 times per month, daily), duration of use (<20 years, ≥20 years) and lifetime number of applications (<3600, ≥3600). They also assessed for reporting biases and the effect of stimulant reporting because of the filing of class action lawsuits.

The median duration of body powder use in both cases and controls was 20 years and body powder use were reported among 52.9% of controls. After adjusting for age at diagnosis/interview, study site, education, tubal ligation, parity, BMI, duration of oral contraceptive use, first degree family history of breast or ovarian cancer, and interview year there was a statistically significant increased risk of ovarian cancer with any genital powder use (OR 1.44, 95% CI: 1.11 to 1.86). There was a stronger association for ≥20 years of any genital powder exposure compared with <20 years of exposure and the test for trend was significant (P_{trend} =0.002). Similarly, the ORs for association between daily any genital powder users and EOC were larger in magnitude than never users, and the test for trend was significant (P_{trend} <0.01) There was also evidence of dose-response for any genital powder for the cumulative number of life-time applications with a higher risk among those with lifetime applications ≥3600; the test for trend was significant (P_{trend} <0.01). A stronger association was reported among post-menopausal women who used HRT compared to non-users. There was also an increase associated with non-genital powder exposure (OR 1.31, 95% CI: 0.95-1.79) which was not statistically significant. There was no evidence of statistically significant increased risk with "only" non-genital users and serous ovarian cancer but was statistically significant increased for non-serous ovarian cancer.

Limitations include the assessment of data by self-report. The underreporting of powder use in the abdomen which may reach the genital area may have resulted in a spuriously increased risk among "only" non-genital users or such an effect may be specific to African-American users. Although there was some evidence that there was more reporting of genital powder use

after class action lawsuits in 2014, recall bias alone is insufficient to explain these findings because there was a statistically significantly increased risk both before and after 2014.

29. In 2016, Cramer et al. (54) included 2,041 ovarian cancer cases from Eastern Massachusetts and New Hampshire as part of the Nurses' Health Study and the Ovarian Cancer Association Consortium. Pathology reports were reviewed to confirm diagnosis. The population was primarily white with less than 30 participants who were African Americans, Hispanics, Asians, or other race/ethnicities. Controls were identified through random digit dialing, driver license and town-resident lists and were frequency matched to cases by age and residence. Talc exposure was determined through in person interviews with a reference point 1 year prior to diagnosis or date of interview (for controls). Subjects were asked whether they regularly or monthly applied powder to the genital or rectal area, or on sanitary napkins, tampons or on other non-genital areas. Talc exposure was reported as personal use, potential exposure with no personal use (diaphragm, condoms, partner use), any genital powder use, type of genital powder use (cornstarch, baby powder, other), age of first use, time since exposure ended, frequency of use, years used, months per year of use, and total applications. Lifetime application was assessed by multiplying frequency of application per month with months of exposure. This was divided by 360 to yield talc years which were partitioned into separate quartiles for dose-response analysis. The study adjusted for a variety of confounders, with adjustments for age, study center, study phase, race, BMI, height, weight, parity, breastfeeding, oral contraceptive use, IUD use, ovulatory cycles, endometriosis or painful periods, Jewish ethnicity, family history, personal history of breast cancer, menopausal status, current smoking, ever smoked, asthma, alcohol consumption, and acetaminophen, aspirin or ibuprofen use.

Any genital powder use was reported in 26% of controls. The women who exclusively used cornstarch were considered unexposed. Most talc users began talc exposure around the age of 20. Overall, genital powder use was associated with a statistically significant increased risk of ovarian cancer (OR 1.33, 95% CI: 1.16-1.52) adjusted for age, study center and phase. BMI, smoking and alcohol use did not alter the association by more than 10% suggesting a lack of confounding. <u>Most women reported using Johnson's Baby Powder and Shower to Shower with a trend for increasing risk by talc years. The trend for frequency of use was significant, but the trend for duration of use was flat.</u> The talc ovarian cancer association was largely confined to premenopausal women and post-menopausal women with hormonal therapy. Sensitivity analysis indicated that the risk of misclassification of exposure in controls would have to very high (18%) to nullify the increased risk shown in the study. No data is available

on the extent of misclassification of talc exposure. Although some amount of misclassification is possible in retrospective studies, such a large amount is unlikely as shown by estimates from other analogous exposure-outcome association such as alcohol and breast cancer in the Nurses' Health Study. (114).

IX.III Cohort Studies. I will discuss the cohort studies below. However, it is important to emphasize that none of the cohort studies discussed below were designed to evaluate the association between talc use and ovarian cancer at the time of cohort assembly. In other words, evaluating the association between talc use and ovarian cancer was not the a-priori primary objective of the study but evaluated as a subsequent hypothesis, with its inherent limitations. For example, the NHS cohort was assembled in 1976 but data on talc use was not collected until 1982. (14). In contrast the primary objective of most case-control studies noted above was to evaluate the risk of ovarian cancer associated with talc use.

IX.III.I. In 2000, Gertig et al. (14) reported on an analysis from the U.S. Nurses' Health Study. 121,700 registered nurses were enrolled in the study; 78,630 were included in the cohort study; and 307 cases of ovarian cancer in 11 states. Notably, the Nurses' Health Study was a broad-based study of women's health. Ovarian cancer information was obtained through a questionnaire mailed to married female nurses 30-55 years which were updated every 2 years. Talc exposure was obtained from a survey question which asked "Have you ever commonly used talcum, baby powder, or deodorizing powder a) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or b) to apply on sanitary napkins? No, Yes." Frequency was thus both reported as an "ever, never" metric as well as applications per week but duration of use was not recorded. Information gathered by a questionnaire requesting information on perineal talc use was ascertained only in 1982, and never updated during follow-up. Medical records were obtained for women reporting diagnoses of ovarian cancer or those participants who died (mortality follow up was 98% complete). Histologic subtypes of ovarian cancer were determined from pathology reports and classified as serous (cystadenocarcinoma and papillary adenocarcinoma), mucinous (mucinous papillary adenocarcinoma and adenocarcinoma), endometrioid (clear cell and mixed epithelial), and borderline. Cases of epithelial ovarian cancer (ICD 183.0) confirmed by medical record review or death certificate between 1982-1996 were included in the analyses. Participants who did not respond to the 1982 question on talc use were excluded, as were participants with cancer other than non-melanomatous skin cancer, bilateral oophorectomy, ovarian removal and those with radiation therapy. They included 307 cases of ovarian cancer among 984,212 person-years of follow up (0.03% PYs or 31.2/100,000 PYs). Information on covariates was obtained from the

biennial questionnaire and included oral contraceptive use, tubal ligation, parity, family history (not asked until 1992), smoking and BMI. Age adjusted incidence rates were calculated after adjusting for covariates above, as well as age at menarche, duration of breast feeding, age at menopause. 40.4% (n=31789) reported ever talc use of which 14.5% were ever daily talc users. Women who were talc users and did not have a tubal ligation had no increased risk of epithelial ovarian cancer with talc use- no evidence of interaction. There was an increased risk for histologic subtypes of ovarian cancer with talc use which was not statistically significant (RR 1.09, 95 % CI: 0.86-1.37) after adjusting for age, duration of oral contraceptive use, body mass index, tubal libation history, smoking status, and postmenopausal hormone use. While daily talc use on perineum (RR 1.12, 95% CI: 0.82-1.55) or use less than once/week (RR 1.14, 95% CI: 0.81-1.59) was associated with an excess risk which was not statistically significant, the point estimates for talc use on perineum 1-6 times/week (RR 0.99, 95% CI: 0.67-1.46) and on sanitary napkins (yes/no) (RR 0.89, 95% CI: 0.61-1.28) were lower than 1, and these confidence intervals may not rule out an increased risk. Importantly, there was a statistically significant increased risk for ever talc use for serous invasive cancers (RR 1.40; 95% CI: 1.02–1.91). For women who reported ever daily use, the RR for serous invasive cancer was 1.49 (95% CI: 0.98-2.26). The RRs for ever-users of less than 1 time/week and of 1-6 times/week were 1.29 (95% CI: 0.81-2.04) and 1.49 (95% CI: 0.77-2.11), respectively (P_{trend}=0.05). Women above age 45 in 1982 who reported ever talc use had a higher risk of serous invasive cancer (RR 1.51, 95% CI: 1.07-2.15).

The strengths of the study include the prospective design which reduces the risk of recall bias. The relatively short follow up period may have been unable to determine ovarian cancer. The NHS cohort was not primarily designed to evaluate the association between talc and ovarian cancer. Further, as discussed above, determining "never" use based only on a one-time question near the start of the study (14 years prior to terminating the study in 1996) introduces unidirectional "behavioral change" bias, likely misclassifying some "ever" users who used talc during the study as "never" users; and biased the findings towards the null. The exclusion of prevalent cases of ovarian cancer allows one to determine the influence of exposure on incident ovarian cancer, it also introduces an element of selection bias. Of the initial cohort of 121,700 volunteers, only 78,630 women were enrolled. It is not known whether any (or how many) of the 43,000 excluded women had ovarian cancer, nor whether any (or how many) of any such ovarian cancer volunteers excluded were talc users. They could not determine the intensity of exposure as they had no information on duration of talc exposure, or number of life-time applications or the age at which talc was initiated. The study was not a "new user design" and

used prevalent rather than incident users, and is susceptible to "prevalent user biases." (15) Prevalent users are "survivors" of the early period of talc use, which can introduce substantial bias if risk varies with time. This may bias findings towards the null due to the "depletion of susceptibles." They had no data on the intensity of exposure because there was no data on the duration of talc use, or number of life-time applications. The analysis on tubal litigation could not determine whether talc use was initiated after tubal ligation. Any such misclassification of exposure is also likely to be non-differential and bias towards the null.

As a continuation of the Nurses' Health Study, in 2010, Gates et al. reported on 924 cases of the ovarian cancer as part of Nurses' Health Study with ovarian cancer confirmed by a gynecologic pathologist review of medical records. (92). They evaluated the findings between risk factors for ovarian cancer and histologic subtypes of ovarian cancer and information on talc exposure was collected through biennial questionnaires. Talc use was reported as either greater than or less than once a week. After adjusting for body mass index activity, past smoking, current smoking, family history of breast or ovarian cancer, age, parity, parous status, breastfeeding, oral contraceptive use, tubal ligation, hysterectomy, age at natural menopause, and estrogen use they reported a non-significantly increased risk of all epithelial ovarian cancer (RR 1.06, 95% CI: 0.89 to 1.28) with genital talc use > once/week compared to < once a week. Although the estimates for the RR were higher for mucinous subtype (RR 1.50, 95% CI 0.84-2.66), there was no evidence of interaction across the subtypes ($P_{heterogeneity}$ =0.55) in this analysis. The strengths and weaknesses of this study are largely like the Gertig analysis of the NHS cohort above, with the additional limitations in the low number of cases (only 29 cases of epithelial ovarian cancer among genital talc users in 108, 870 women).

IX.III.II. In Houghton et al. (17) reported on finding from the Women's Health Initiative Observational Study (50-79 years at enrollment and post-menopausal). Among the 93,676 volunteers, only 61,576 participants were in the study cohort, and 429 adjudicated incident ovarian cancer (0.7%). Participants completed annual mailed questionnaires. Participants with bilateral oophorectomy, unknown number of ovaries, history of cancer (except non-melanomatous skin cancers were excluded). Perineal powder exposure (rather than specifically talc use) was obtained via self-report at baseline, and not updated during follow-up. Participants were asked whether powder had been used on genital areas, diaphragm or sanitary napkin or pad. If the participant answered affirmatively, there were further questions regarding duration of use where participants indicate use for less than 1 year, 1-4 years, 5-9 years, 10-19 years, or 20

or more years, but frequency of use was not recorded. The area of use was assessed dichotomously, and duration of use was categorized as never, 9 years or less and 10 years or more for analysis. Analysis was conducted for ever perineal powder use (ever use for any of the three categories) and duration for any powder use (maximum duration of any single area of application). Cancer cases were self-reported and confirmed through medical records including pathology reports. Data on covariates for age, race, education, alcohol, metabolic equivalents, smoking, recreational physical activity, oral contraceptive use duration, hormone replacement therapy, family history, age at last birth, BMI, self-reported family history of ovarian cancer were evaluated. They also evaluated reproductive factors such as age at menarche, age at menopause, age at first birth, age at last birth, parity, breastfeeding duration, history of tubal ligation, hysterectomy, irregular cycles, endometriosis. The covariates were obtained at baseline and not updated. The proportional hazards analysis was conducted to examine the risk of ovarian cancer and proportional hazards was tested using Schoenfied residuals. Participants with other cancers were still considered at risk for ovarian cancer. Covariates were selected for the multivariate analyses, if they had P-values of less than 0.1 during the backward regression until they had a parsimonious model. Additional variables from the literature were also included although they were not statistically significant. They analyzed ever perineal use, perineal use by application area, duration of use and combinations. Test for linear trend was evaluated across duration categories by modeling categories as continuous variables.

The average age of participants was 63.3 years at baseline with 12.4 years of mean follow-up. Most participants were white and were obese. Approximately 52.6% of the population reported ever use of perineal powder. Ever users were more likely to be heavier, used oral contraceptives and/or diaphragms. Perineal use of powder was associated with a 12% excess risk which was not statistically significant ($HR_{adj,}$1.12, 95% CI: 0.92- 1.36) whereas point estimates for use on sanitary napkins and diaphragms were lower than 1 but could not rule out an excess risk. Duration of perineal, sanitary napkin or diaphragms were not associated with ovarian cancer.
Strengths include the prospective design which reduces the risk of recall bias. Limitations includes the lack of information on whether the perineal powder use constituted talc use, and the inability to measure the frequency of exposure. It is possible that the analysis by duration included infrequent long duration users with short term frequent users which may result in bias towards null. Since exposure was not updated during follow-up, some never users who became ever users were misclassified as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer introduced an element of selection bias. Of the initial cohort

of 93,676 volunteers, only 61,576 women were enrolled; 10,622 volunteers who had already developed cancer at baseline were excluded. It is not known whether any (or how many) of these excluded women had ovarian cancer, nor whether any (or how many) were talc users. The inclusion of "prevalent users" rather than "incident users," leads to depletion of susceptibles and may bias findings towards the null. Data on covariates was not available after baseline resulting in the potential inclusion of participants (e.g., oophorectomy) not at risk of ovarian cancer and resulting bias towards the null. The generalizability of the study findings to younger pre-menopausal women is also unknown as the study findings are limited to older post-menopausal women (average age =63.3 years).

IX.III.III. In 2016 Gonzales et al. (93) examined the relationship between douching, talc use, and ovarian cancer among 50,884 women aged 35-74 years of age (84 % white and 64% post-menopausal) who had never had breast cancer but had a full or half-sister who with breast cancer. They excluded participants with bilateral oophorectomy and ovarian cancer. Among 41,654 participants 154 incident ovarian cancers (n=135 ovarian cancers) were reported (0.3%). Participants completed a telephone interview which included questions about reproductive history (oophorectomies), health and lifestyle and use of personal care products before enrollment, including the use of douching and use of genital talc applied as a powder or spray applied to underwear, sanitary napkin, diaphragm, cervical cap, or vaginal area. The frequency of use was categorized as no use, less than once a month, 1-3 times per month, 1-5 times per week, > 5 times per week, but duration of use was not recorded. As with the WHI and Nurses' study exposure was only measured at baseline and not updated during follow-up. Updated information on oophorectomy was collected during follow-up and information on cancer cases was collected via annual health update. Data on 37.6% of ovarian cancer cases was available only by self-report and the remainder confirmed by medical record review or death certificate. Cancer cases included tumors of the ovary, fallopian tubes, peritoneum, or of uncertain origin. Those who were BRCA1 or BRCA 1 positive test or those who had a sister with a positive test but had no report of negative test were considered BRCA positive. Cox proportional hazards analysis was conducted until diagnosis of ovarian cancer, oophorectomy, censoring or death. Generalized estimation equations was used to account for familial clustering at baseline. The proportional hazards assumption was evaluated by the goodness of fit test. A joint analysis of talc and douching use was also conducted. The included covariates were patency (yes or no for tubal ligation or hysterectomy), menopausal status, duration of OC use (none, < 2 2 to <10, 10 or more years), parity (yes/no) race and BMI.

The median duration of follow up was only 6.6 years. The average age was mean 57.8 years for cases. These cases were more likely to have a family history of ovarian cancer and carry a BRCA1 or BRCA2 mutation. More non-cases than cases used oral contraceptives. Talc use was only reported by 12% of cases and 14% of non-cases. Talc users were more likely to have BMI >30 kg/m^2. Talc use in the last 12 months after adjusting for race, BMI, parity, duration of oral contraceptive use, baseline menopausal status, and patency, was not associated with a statistically significant increased risk of ovarian cancer (HR 0.73, 95% CI: 0.44-1.20], but could not rule out an excess risk. There was no change in estimates when adjusted for douching. Douching at baseline, more common among talc users, was associated with increased risk of ovarian cancer (HR: 1.8 95% CI: 1.2-2.8).

There were significant limitations to the study. The authors acknowledge that an important limitation of their study was that they collected douching and talc information for the year before the study and did not account for the latency. As with the other two cohort studies, the Sister Study was limited by the issue of selection bias through the exclusion of women who had already developed ovarian cancer (and who could also have been lifetime talc users). Secondly, the Sister Study was vulnerable to behavioral change bias. The bias towards the null of this inaccurate assessment of "ever" user status prospectively, at the start of the study, was compounded by the fact that it was also vulnerable to retrospective inaccuracy, because it was based only on the 12 months preceding baseline. Thus, a participant who had last used talc 13 months before baseline would be categorized as a never-user, as would a participant who started using talc after baseline. Thirdly, the Sister Study's median follow-up of only 6.6 years is likely insufficient to detect any risk of ovarian cancer which likely takes more than 6.6 years to develop. The study also suffered from the limitations of prevalent user biases. Additionally, exposure was measured as ever/never use in 12 months prior rather than total applications resulting in non-differential misclassification towards the null. Data was only available by self-report on the diagnosis of ovarian cancer for many cases (37.6%) resulting in misclassification of outcome, which was likely non-differential and may bias findings towards the null. The study reported the lowest rate of talc use among the cohort studies (13.8%), further compounding the limited statistical power due to a short duration of follow-up. The generalizability of these findings is also limited as they included women without breast cancer who all had a family history of breast cancer and_may be at a higher risk (60%). The missing data were not missing at random and unclear whether analyses were adjusted for missing data. The authors concluded that the study

could not exclude a increased risk despite these findings. The study findings are limited to the predominant cohort of white post-menopausal women who constituted the majority of participants.

IX. IV. Summary of Findings from Epidemiological Studies.

1. The cumulative evidence from these studies demonstrates a statistically significant increased risk of ovarian cancer associated with perineal talc powder use which has been independently replicated by several investigators in different populations, different settings, across different sources using different study designs and time periods. Slight differences in magnitude of risk among these studies may reflect differences in inclusion or exclusion criteria and the accumulation of evidence over time and some variation due to chance. The updated meta-analyses in 2018, which have included all the studies, reported a statistically significant increased risk of perineal talc use and ovarian cancer, (41, 42), with little evidence of statistical heterogeneity or publication bias. The case-control studies provided 13,421 cases compared to 890 cases in the cohort studies. (42). Most case-control studies demonstrate an increased risk of ovarian cancer associated with talc use with an OR between 1.3 and 1.6, even after adjusting for various risk factors.

2. Meta-analysis which evaluate the association between perineal talc use and ovarian cancer have consistently shown an increased risk of ovarian cancer, (39, 41, 42, 73, 79), including pooled analysis using individual participant data. (10). My conclusions about the causal increase in the risk of ovarian cancer associated with talc exposure are heavily weighted by recent cumulative meta-analysis published in 2018, (41, 42). These meta-analyses provide the most comprehensive evidence base given the size of the study database and their methodologic superiority as assessed by the AMSTAR rating above. (Table 1). Also, importantly, there is no meta-analysis which has reported a statistically significant decreased risk of ovarian cancer with talc.

3. The only case-control study in which point estimates are below one was limited by the poor choice of controls and very high non-response rates. Despite these limitations it could not rule out a 21% increased risk of ovarian cancer associated with talc use which is not inconsistent with other studies. (86). Although the exposure rate to talc in the case-control studies has been variable in the control group from 5%-45%, this reflects the varying practices in the use of talc rather than the lack of an increased risk of ovarian cancer with talc use.

4. Although all studies are at potential risk of outcome misclassification, most of the studies used histologically verification for the diagnosis of ovarian cancer. Any such potential

misclassification of outcomes is likely to be non-differential and would have biased the findings towards the null.

5. There is no reason to believe, from the studies, that ovarian cancer would result in talc use, so the temporality of the association is established.

6. Case-control studies are susceptible to recall bias particularly when data on exposure are self-reported. However, several studies have included these questions on talc exposure as a part of larger questionnaires on other risk factors minimizing the possibility of recall bias. Recall bias is less likely to occur for chronic daily exposures such as talc as compared to intermittent short exposures. Further, recall bias is equally likely to affect other histologic types of ovarian (and endometrial) cancer but here the increased risk was limited to only epithelial ovarian cancer in most studies. Finally, the findings that only perineal talc use was associated with ovarian cancer but not with non-genital talc use argues against recall bias alone as a potential explanation of these findings.

7. Confounding is one potential explanation for these findings. However, several case-control studies adjusted for major confounders including the more recent case-control studies. (54). Although residual confounding is always possible in an observational study, studies that have reported adjusted and non-adjusted findings have reported similar results minimizing the impact of residual confounding. (41). Although there are some risk factors for ovarian cancer (e.g., genetic risk factors, family history, obesity and reproductive history), for any of them to be confounding to an extent that could account for the positive relations that have been reported, they would have to be strongly correlated with talc use. Family history, ethnicity, obesity and some reproductive risk factors are positively associated with the risk of ovarian cancer, but the magnitude of these associations does not appear high enough to introduce enough confounding, even jointly, to explain completely the positive association. To invalidate the statistically significant findings of an increased risk of ovarian cancer from the studies, one would have to postulate a degree of selection, recall bias and confounding pervasive across different time periods, different populations which is highly implausible.

8. Case-control studies are also at risk of selection bias which may introduce bias in both directions. As opposed to hospital-based controls, which may be less susceptible to selection bias, the population-based case-control studies have consistently showed a higher estimate of increased risk of ovarian cancer associated with talc use.

9. Reverse causality, where the diagnosis of ovarian cancer results in perineal use of talc, may be one possible explanation of the nonsignificantly increased risk in the group exposed to perineal talc. However, this is also likely minimal in the case of ovarian cancer in which most

cases present at advanced stages with abdominal bloating, and vaginal symptoms only occur in a small minority of cases.

10. One of the cohort studies reported an increased risk with perineal talc exposure and serous invasive cancer (14). The pooled results from all three cohort studies, reported an excess risk of ovarian cancer, (42) which failed to reach statistical significance because of several limitations. The duration of follow up was limited resulting in low number of events and inadequate statistical powder. The only cohort study which reported an inverse association between perineal talc use and ovarian cancer included several other cancers beyond the ovary (such as peritoneum, endometrial) (93), which may have diluted an increased risk. It had a very short duration of median follow up of approximately 6.6 years which is insufficient to ascertain the development of ovarian cancer. Since talc induced carcinogenesis occurs via a foreign body mechanism, the latency period required to demonstrate such an effect is long. Despite these limitations, the upper bounds of the confidence intervals exceeded one and could not rule out an increased risk of ovarian cancer with perineal talc use. The cohort studies were at risk of significant other biases. Exposure was measured at baseline and not updated during follow-up (14, 17), which may have misclassified those participants at baseline who were never users but used talc during the study as never users resulting in a bias towards the null. The exclusion of prevalent cases of ovarian cancer (some of whom may have been exposed to talc) may also bias their findings. (14, 17) The cohort studies were also susceptible to "depletion of susceptibles" biasing their findings towards the null. None of the cohort studies were primarily designed to study the association between genital talc use and ovarian cancer as their primary objective. Despite these limitations, the meta-analysis of cohort studies demonstrated a statistically significant increased risk of serous invasive ovarian cancer.

11. Ascertaining *dose response* relationship with talc and ovarian cancer is difficult because of the challenges in quantifying talcum powder use usually collected by self-reported data (frequency, amount and duration), timing and patterns of use (e.g. douching), and other individual factors (e.g. co-existence of inflammatory conditions such as endometriosis and or vaginal bleeding) resulting in differences in measurement of exposure across studies. The dose response depends on both the amount of talc exposure, the frequency of talc uses and the duration. It is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an ''application of talc.' Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open, the age of initiation of talc use since the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (79). The presence of other risk factors

such as post-menopausal status, cancers other than invasive serous ovarian cancer may make it difficult to ascertain a dose-response relationship among older post-menopausal. The lack of statistical trend (58, 60) in some earlier studies may reflect some of these challenges as well the lack of a monotonic dose response effect. The exposure-response data need to be interpreted in the context of mechanistic studies which report that talc accelerates the development of ovarian cancer in susceptible individuals through accelerating the redox state in epithelial ovarian cancer cells. (49). Thus, an assessment of the gradient through a monotonic dose-response curve may not provide a complete picture of the biological gradient. It unclear why nature would mandate an increasing mono-tonic dose-response mechanism for causation, and some have argued that among Bradford-Hill viewpoints it is difficult to know how dose-response should be modelled. (50). Cumulative lifetime exposure may be a more appropriate measurement of exposure given the inflammatory mechanisms by which talc induces the development of ovarian cancer. It is important to recall that if the carcinogenicity of talc induced ovarian cancer most likely resembles that of asbestos induced mesothelioma (with which it shares histologic similarities), asbestos induced mesothelioma does not have a dose-response relationship. In the case of asbestos induced mesothelioma, latency may be more important whereas in the case of talc induced ovarian cancer induced by inflammation latency may be of lesser importance.

12. Despite these challenges, several studies have shown evidence of dose-response as measured by an increased risk with increased frequency (51-55) or increased duration, (52, 54)or combination of frequency and duration of exposure. (48, 54). Some studies show a exposure-response trend, (54) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). In the individual participant data meta-analysis a significant increase in risk with an increasing number of genital powder applications was found for nonmucinous epithelial ovarian cancer when nonusers were included in the analysis, but no significant trend was seen when analyses were restricted to ever users. (10) Importantly, the most recent meta-analysis reported an evidence of dose-response with risk being higher among those with >3600 applications of talc compared to participants with <3600 applications. (42) Both of these categories of exposure were associated with an increased risk of ovarian cancer. None of the cohort studies were able to conduct meaningful dose-response analysis because they did not collect data either on duration, (14, 93) or frequency of exposure. (17).

X. BIOLOGICAL MECHANISMS OF TALCUM POWDER INDUCED OVARIAN CANCER.

Although not an absolute requirement for determination of causation there are multiple well-established biological and molecular mechanisms by which talcum powder products induce ovarian cancer. The key routes of exposure and biological mechanisms are noted below.

***X.I. Retrograde Migration of Talc Particles*.** Genital talc can migrate up to the fallopian tubes and ovaries and talc particles have been detected within the ovaries of women who report perineal talc use. Heller et al. detected talc in the ovaries of 24 women undergoing incidental oophorectomy demonstrating that it can reach the upper genital tract (64) although the fact that talc particle counts were unrelated to reported levels of perineal talc exposure reflects the challenges in measuring exposure to talc. Talc has been found deeply embedded within ovarian tumors, (65) and subsequent studies have confirmed that these are not due to contamination. (94). Talc has also been demonstrated in pelvic lymph nodes of women with perineal talc exposure.(66). Supportive evidence of migration comes from studies showing retrograde migration of additional particles such as starch after gynecological examination, (68) findings of a decreased risk of ovarian cancer with tubal ligation and hysterectomy in case-control studies, (87) and meta-analysis, (115) which may minimize exposure to inflammatory particles. Although an industry funded study performed by the Cosmetic, Toiletry, and Fragrance Association failed to detect translocation of "measurable quantities of talc' in monkey models, (67) the timing and techniques of assessment and intraspecies differences could not rule out migration of talc particles. The FDA response to Citizen's Petition 2014 concluded the *"potential for particles to migrate from the perineum vagina to the peritoneal cavity is indisputable'*. Johnson & Johnson and IMERYS documents also acknowledge migration. In one document it was stated, "A review of the literature suggests that it is biologically plausible for talc particles to migrate from the vagina to the peritoneal cavity and ovaries following perineal application." (63, 116).

***X.II. Inhalation of Perineal Talcum Powder*.** Inhalation of talcum powder is another potential route of exposure that is biologically plausible and can cause inhaled fibrous talc (and asbestos) fibers to reach the ovary and thus increase the risk of ovarian cancer in women using these products. Approximately 50 percent of talc particles in commercially available talcum powder are less than 10 microns in size, (117) which have the potential for inhalation and reach the alveolar regions of the respiratory tract. (118) Asbestos fibers can pass from the alveoli to the

lung interstitium, from which they can travel via the lymphatic system to the bloodstream and other organs including ovaries. (119, 120) Inhaled fibrous talc shares extensive physical and chemical similarities with asbestos, and inhaled fibrous talc generated from perineal application may also reach the ovaries by inhalation. This mechanism was confirmed in a September 2017 study, "Below the Waist Application of Johnson & Johnson Baby Powder," Longo, et al. showed that normal application of Johnson's Baby Powder can produce airborne asbestos and talc fibers which could be inhaled. (70).

X.III. Talcum Powder Induced Inflammation and Alteration of Redox Potential. Inflammation has long been understood to be an important mechanism underlying the development of ovarian cancer. (61). Inflammation may underlie ovulatory events because an inflammatory reaction is induced during the process of ovulation. Risk factors for ovarian cancer include endometriosis (i.e., ectopic implantation of uterine lining tissue) and pelvic inflammatory diseases (PID). (121). PID was associated with an increased risk of borderline ovarian tumors, particularly among women who had had multiple episodes of pelvic inflammatory disease in a meta-analysis. (122). Consistent with the inflammatory mechanism for ovarian cancer, a prospective nested case-control study from the Prostate, Lung, Colorectal and Ovarian Cancer has also shown that global markers of inflammation such as C-reactive protein, Interleukin L-1α, Interleukin-8 and Tumor Necrosis Factor-α are associated with a significantly increased in the risk of ovarian cancer. (123). Supportive evidence for the role of inflammation also comes from a meta-analysis showing a decreased risk of ovarian cancer with tubal ligation and hysterectomy. (115). Studies have demonstrated increased risk of ovarian cancer with talcum powder use, and increased risk of ovarian cancer with endometriosis. (87). This risk is 3-fold higher among women exposed to talc who have endometriosis. (48).

Oxidative stress in the form of reactive oxygen species (ROS) and reactive nitrogen species (RNS) plays a role in the pathogenesis, neo-angiogenesis (formation of new vessels) and the dissemination of both early and late stage epithelial ovarian cancer. (124, 125). Epithelial ovarian cancer cells manifest a persistent pro-oxidant state characterized by upregulation of certain key oxidant and downregulation of key antioxidant enzymes, (125) and the presence of oxidative stress triggers cancer cells to favor anaerobic metabolism. Oxidative stress induces phenotypic modification of tumor cells by altering cross-talk between tumor cells and surrounding stroma. Talc can alter this redox state and cause a marked increase in mRNA levels of the prooxidant enzymes, iNOS (nitrous oxide) and MPO (myeloperoxidase) in talc treated ovarian cancer cells as compared to control as early as 24 hours in all doses, (49) as well as a marked decrease in the

mRNA levels of the antioxidant enzymes catalase CAT, glutathione peroxidase (GPX), and superoxide dismutase (SOD3) providing a mechanism by which talcum powder products can induce the development of ovarian cancer.

Cancer antigen [CA-125] a tumor marker secreted by the epithelial cell for monitoring recurrence after treatment of ovarian cancer, was elevated when both normal ovarian cell lines [1.7 +/- 0.5-fold] and ovarian cancer cell lines [1.4±0.5 and 4.4±0.5-fold increase in OV90 and TOV-21G EOC cell lines] were exposed to talc, providing another molecular mechanism by which talc can increase the risk of ovarian cancer. (106).

Talc has been shown to increase proliferation, induce neoplastic transformation and increase ROS generation time-dependently in the normal human epithelial and granulosa ovarian cells and dose-dependently in the polymorphonuclear neutrophils. (71). In studies of human mesothelial cells, both nonfibrous talc and asbestos have shown evidence of genotoxicity. (109) Some have suggested that perineal talc use may also increase risk of ovarian cancer by the induction of anti-MUC1(monoclonal antibodies) possibly via heat-shock protein, (72) although the data are not definitive. (101).

X.IV. Carcinogenicity in Animal Studies. Among animal studies a study among rats demonstrated the development of papillary changes after intrabursal injection of talc. Such papillary changes may be precursors of serous papilloma precursors of epithelial cancers. (107). Another 2-year inhalation study with cosmetic grade talc in rats and mice showed evidence of carcinogenic activity in male (an increased incidence of pheochromocytomas of the adrenal gland) and female (increased incidences of alveolar/bronchiolar adenomas) rats and carcinomas of the lung and pheochromocytomas of the adrenal gland. (108). There was no evidence of carcinogenicity in mice. However, limitations of this study include the lack of a suitable control (e.g. titanium dioxide), alternative explanations of these findings via particle overload, (127) and the fact that ovulatory patterns in rats are not fully applicable to humans.

X.V. Presence of Asbestos and other carcinogens in Talcum powder products. In assessing the biological plausibility of talcum powder products as a cause of ovarian cancer, it is important to consider the constituents of talcum powder products including whether it contains known or suspected carcinogens. The presence of asbestos in talcum powder products can and does provide a plausible biological explanation of the development of ovarian cancer. (36, 37).

Occupational exposure to asbestos is a well-established causal agent for the development of pleural and peritoneal mesothelioma, larynx and ovarian cancer. (36, 127). Talc and asbestos also share chemical similarities. The carcinogenicity of asbestos relies on shape of particles with long thin fibers-such as those occurring in crocidolite asbestos being particularly carcinogenic. Although talc consists primarily of platy talc, it may also contain fibrous talc or other asbestiform minerals. Epithelial ovarian cancer, one most closely associated with talc, histologically most closely resembles mesothelioma providing further evidence of biological mechanisms. As Huncharek notes in their meta-analysis of ovarian cancer associated with talc dusted diaphragm meta-analysis on page 427 "*If one is exposed to a mixture of talc and asbestos, it is reasonable to expect a carcinogen effect as it contains a known carcinogen.*" (13). In addition talcum products contain fibrous talc, heavy metals and fragrance ingredients which are known or suspected carcinogens. (26, 33, 35, 36). Like the presence of Asbestos Fibers, the presence of these known or suspected carcinogens provide a plausible biologic explanation for the increased risk seen in the epidemiologic studies.

XI. ASSESSMENT OF CARCINOGENECITY OF TALC BY THE IARC IN 2006.

The International Agency for Research on Cancer (IARC) expert panel evaluates the carcinogenicity of various products using the following criterion after review of animal studies, experimental studies and epidemiological data. (128). The data is examined to determine whether there is *sufficient evidence, limited evidence, inadequate evidence, or evidence suggesting lack of carcinogenicity* for both cancer in humans and animals, respectively. The mechanistic and other relevant data are examined to *identify established and likely mechanisms and determines whether each mechanism could operate in humans*. The agents are then classified into several groups. Group 1 are agents *carcinogenic* to humans (e.g., asbestos,) (37), Group 2A are agents *probably* carcinogenic to humans, Group 2B *possibly* carcinogenic to humans, Group 3 agents which are *unclassifiable* and Group 4 agents which are *probably not carcinogenic* to humans.

In 2006 IARC concluded that perineal use of talc not containing asbestos or asbestiform fibers was possibly carcinogenic to humans (129) based on *limited evidence in humans for the carcinogenicity of perineal use of talc based body powder and the limited evidence in experimental animals for the carcinogenicity of talc* (93) (Group 2B-b). (38). Although a positive association has been observed between exposure to the agent and cancer for which causal interpretation is considered by the Working Group to be credible, but chance, bias, or confounding could not be ruled out

with reasonable confidence. For purposes of their evaluation, IARC considered 19 case-control studies and 1 cohort study. (14). The Working Group concluded that 8 of the more informative case-control studies (as well as most of the less informative ones) showed a consistent excess risk in the order of 30-60%. The cohort studies neither supported or refuted the evidence from case-control studies.

The IARC assessment was carried under the assumption that talcum powder products did not contain asbestos based on the published findings at the time- an assumption that is not supported by current data. In such a case, talcum powder products would be unequivocally classified as a Group 1 carcinogen like asbestos. Importantly, even absent a finding of asbestos in talcum powder products, the consistent cumulative evidence of peritoneal use of talcum powder products demonstrates an increased risk of ovarian cancer. Several *new systematic reviews based on recently published studies have further added to the accumulating evidence on an increased risk of ovarian cancer with talc use.* (10, 41, 42). *There is now further evidence of exposure response* relationships, with measured by an increased risk with increased duration (52, 54) or combination of frequency and duration (48) and the most updated meta-analysis show evidence of duration dose and responsiveness. (42). Finally, in addition to the epidemiologic evidence there is evidence from toxicology , molecular biology and other mechanistic data which supports my opinions .

XII. COSMETIC EXPERT REVIEW PANEL REPORT.

For the sake of completeness I also reviewed a report on the safety of cosmetic talc by an industry sponsored panel. (130). The panel was primarily composed of dermatologists, with limited expertise in epidemiology and carcinogenicity. The review was carried out under the flawed assumption that cosmetic-grade talc must contain no detectable fibrous, asbestos minerals and thus limited its assessment to animal and clinical studies on talc that did not contain asbestos, and erroneously concluded that there was no evidence of talc migration. As a result of these serious methodologic shortcomings and funding biases it arrived at its erroneous conclusions that talc was safe for use in cosmetics. (130) As discussed above, the findings of this panel have been superseded by findings from several new epidemiological studies, mechanistic studies and systematic reviews which have further added to the accumulating evidence on an increased risk of ovarian cancer with talcum powder product use.

XIII. ASSESSMENT OF CAUSALITY.

While talc is clearly associated with development of ovarian cancer, we must assess whether the observed association leads to an inference about causation. In 1965, in the President's Address to the newly-established Section of Occupational Medicine of the Royal Society of Medicine, Sir Austin Bradford Hill, Professor Emeritus of Medical Statistics at the University of London, attempted to encapsulate the aspects of a causal relationship, as it was understood at the time. (1). As he described them, they were: 1. strength of association, 2. consistency, 3. specificity, 4. temporality, 5. biological gradient, 6. plausibility, 7. coherence, 8. experiment, and 9. analogy. As Professor Hill explained, no aspect alone is either necessary or sufficient: "What I do not believe . . . is that we can usefully lay down some hard-and-fast rules of evidence that ***must*** be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence . . . and none can be required as the ***sine qua non***." Further, according to Professor Bradford Hill, these are not the only aspects of causation, but they are informative. It must also always be remembered, as highlighted in a recent statement by the American Statistical Association, that a lack of statistical significance does not imply lack of clinical significance (18) – a point also highlighted by Bradford Hill, who noted that while statistical tests can remind us of the role of chance, *"No formal tests of significance can answer those questions."*

With respect to the analysis at issue, that is, the association between talcum powder products and ovarian cancer—the results are not only statistically significant, but, as described above, have been replicated by several independent authors in multiple studies across a range of study designs. The cumulative body of evidence was appraised using the Bradford Hill viewpoints. In this regard, and as described in this report, I put significant weight on the Strength, Consistency, Temporality, Biologic Plausibility, and coherence factors and, to a lesser extent, Gradient (Dose-Response) and Analogy data to support my opinion that Talcum Powder Products can cause ovarian cancer. For the reasons stated below, I do not weigh heavily the Experiment and Specificity data in light of the totality of the evidence supporting a causal inference. My assessment is described below.

<u>1. Strength of Association</u>. This aspect of a causal relationship refers to the degree or magnitude of effect to which the exposure is associated with the outcome. (1). According to Bradford Hill , the more likely the exposure is associated with the outcomes, the more likely is it to be causal. As summarized in the meta-analysis in section above, I conclude that the association of talc with

ovarian cancer shows an approximate 30-60% relative increase in the risk of ovarian cancer, after adjustment for multiple confounders of the talc and ovarian cancer relationship. (10, 42). The strength of the association, replicated in multiple studies, provides evidence in support of a causal association. There are several noteworthy examples of well-established causal relationships (e.g. second hand smoking and lung cancer), (131) where the strength of the association is in the order of 20-40%. Such causal associations can have significant effects on the population if a large segment of the population is exposed, as in the case of air pollutants and myocardial infarction, which are significantly associated with an increase in MI risk with small relative risk (carbon monoxide: 1.048; 95% CI, 1.026-1.070; nitrogen dioxide: 1.011; 95% CI, 1.006-1.016; sulfur dioxide: 1.010; 95% CI, 1.003-1.017; PM_{10}: 1.006; 95% CI, 1.002-1.009; and $PM_{2.5}$: 1.025; 95% CI, 1.015-1.036) but a large population burden because of the large percentage of the population that is exposed. (47). Similarly, 75-100 mg of daily Aspirin has been shown to reduce the risk of cardiovascular events among those weighing 50-69 kg by 25 % [HR 0.75, 95% CI, 0.65-0.5] (132) in an individual participant data meta-analysis of randomized controlled trials. An increment of one serving a day of fruit and vegetables reduced all-cause mortality by 5% (HR 0.95 95% CI: 0.92 - 0.98) in a meta-analysis of cohort studies. (133). As discussed below, I place significant weight on the fact that studies demonstrate a strong association between talcum powder use and ovarian cancer and show consistency of the data.

2. Consistency. This viewpoint assesses whether the finding is repeated in different settings, place and time. (1). As shown in detail above, the direction and strength of association of talc and ovarian cancer is generally consistent across studies, including observational studies of various designs and their meta-analysis, and observational studies. These studies have been conducted in different clinical settings across the world, with different duration of follow up and the cumulative evidence has consistently shown a significantly increased risk of ovarian cancer with the use of talcum powder products. As expected, there are slight differences in the point estimates which reflect differences in study population with nearly all point estimates showing a direction of increased risk of ovarian cancer. The confidence intervals, however, across study designs overlap, indicating consistent results. I place significant weight on the fact that the consistency and strength of the association found in multiple independent studies demonstrates that the association is causative.

3. Specificity. This viewpoint considers whether the outcome of the disease appears to be specific to the exposure, (1) although since the original publication of the Bradford Hill we know

in most cases, absolute specificity for an exposure outcome association is not generally possible for many diseases, particularly cancer, and not required to provide proof of causation. Even the well-established, causal relationship between cigarette smoking and lung cancer or heart disease is not characterized by specificity. Genetic factors may also play a role in the occurrence of ovarian cancer. As discussed above, the occurrence of ovarian cancer is consistently higher among talcum powder users compared to non-users, even after adjusting for several confounders. I placed less weight on absolute specificity of the association between talcum powder exposure and ovarian cancer given the multi-causal nature of the outcome, particularly in light of the strength and consistency of association factors.

4. Temporality. The temporality viewpoint assesses whether the exposure always predates the development of disease. (1). In each of the epidemiologic studies noted above, talc exposure occurred before the diagnosis of ovarian cancer. Although some have argued that some of the symptoms of ovarian cancer (vaginal bleeding, irritation) may lead to talcum powder use, since most ovarian cancers present with abdominal bloating and advanced stages of the disease it is difficulty to attribute how development of ovarian cancer would lead to talc use (e.g., reverse causality). I placed significant weight that the exposure to talc preceded the development of ovarian cancer in the studies above.

5. Biological Gradient. This viewpoint assesses whether there is a biological gradient or dose-response effect, (1) recognizing that presence of dose-response is not an absolute requirement for causation. In order to determine dose-response, it is necessary first to determine dose. While the presence of a dose-response relationship supports a causal link, the absence of such a relationship does not preclude a causal association. The causal relationship between asbestos and mesothelioma, which most closely resembles the current scenario is not dose-dependent. Assessing dose-response is challenging in the context of perineal talc use for several reasons: first, unlike, say, birth-control pills, the amount of talc powder product use is not fixed, nor is the number of uses per time (day, week, or month). At a minimum, to assess total dose, it is necessary to acquire information about both duration and frequency. Ascertaining a dose-response relationship with talc and ovarian cancer is particularly challenging given that the risk of ovarian cancer may vary with age, premenopausal and post-menopausal status and the presence of other risk factors. The dose-response depends on both the amount of talc exposure, the frequency of talc uses and the duration. The presence of other risk factors such as post-menopausal status, cancers other than invasive serous ovarian cancer and the "depletion of

susceptibles" over time may make it difficult to ascertain a dose-response relationship. Several studies show evidence of dose-response as measured by an increased risk with increased frequency, (48, 51-55) or increased duration, (52, 54, 56) or a combination of frequency and duration of exposure. (52, 54). Some studies have also shown evidence of increased risk with increased number of lifetime applications, (10, 48, 52) which may be a more accurate measure for long term exposure outcome association mediated via inflammation. The most updated meta-analysis show evidence of duration dose and responsiveness, (42) with risk being higher among those with >3600 applications of talc compared to participants with < 3600 applications, although with overlapping confidence intervals. (42). Based on the above limitations with study design to ascertain dose effect, specificity of dosing of talc and the possibility of threshold effect, I find biological gradient less compelling, but still compelling of my causation analysis than the other Bradford Hill overviews as referenced above.

6. Plausibility. Although this is not a requirement for causation, an association that is biologically plausible is more likely to be causal. (1). While this viewpoint only requires biological mechanism to be *plausible*, which is necessarily limited to the state of biological knowledge at the time of assessment, evidence from the literature described in detail in the section in biological mechanisms shows multiple routes of exposure, multiple pathways and multiple mechanism by which talc can cause ovarian cancer. **Section X** demonstrates how talcum powder products can migrate to the ovaries, induce inflammation, alter redox potential resulting in a pro-oxidant state, (49) and act as a mutagen. (109). As a results of the significant body of evidence that has accumulated on biological mechanisms, I place significant weight on the fact biological plausibility provides evidence in support of the causal role of talc in the development of ovarian cancer and there is a highly biological plausible mechanism here for carcinogenicity which supports my opinion.

7. Coherence. This viewpoint assesses whether the cause-and-effect interpretation of data conflicts with the generally known facts of the natural history and biology of the disease. (1). The evidence on the risk of ovarian cancer with talcum powder exposure is consistent with the nature of the disease. Multiple studies suggest that talcum powder products have biological effects which plausibly explain the occurrence of ovarian cancer. Given the biological mechanisms related to inflammation described above, this mechanism and causal association itself fit easily within the current framework of scientific knowledge about the development of

ovarian cancer mediated by inflammation. I placed a significant weight on the coherence of findings in support of the causal role of talc in the development of ovarian cancer.

8. Experiment. Occasionally, in making a causation assessment, it is possible to appeal to experimental, or semi-experimental, evidence. The definitive experimental evidence would be a placebo controlled randomized trial among patients who are assigned to use talc and others who do not use talc in which the outcome of incident ovarian cancer would be actively ascertained. However, such evidence does not exist and would not be ethical nor feasible with a rare outcome such as ovarian cancer with an incidence of 11.4/100, 000 person-years noted above. While there is no randomized controlled trial here, that is common when dealing with a suspected cancer risk. For instance, there is no randomized controlled trial which supports the causal role of smoking in lung cancer. Such a trial to provide absolute proof of harm, which ignores the body of evidence that has accumulated and places patients at risk for developing ovarian cancer raises significant ethical concerns when data from robust observational studies and their meta-analysis have consistently shown an increased risk of ovarian cancer. In the absence of experimental evidence, this overview is weighted as less important than the other more important viewpoints noted above.

9. Analogy. Asbestos has been shown to cause ovarian cancer which offers an appropriate analogy, (40) but this viewpoint was considered less significant than other viewpoints noted above.

XIV. CONCLUSIONS.

Based on my background, training and education as a physician and epidemiologist, review and analysis of the totality of the evidence, using the weight of evidence analysis, including considering and weighting the Hill viewpoints, as described in this report, it is my opinion stated to a reasonable degree of scientific and medical certainty that peritoneal use of talcum powder products can cause ovarian cancer.

Signed this 16th day of November 2018

Sonal Singh

Sonal Singh, MD, MPH

References

1. Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine. 1965;58(5):295-300.

2. Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. Carcinogenicity of some drugs and herbal products. Lancet Oncol. 2013;14(9):807-8.

3. Zorzela L, Loke YK, Ioannidis JP, Golder S, Santaguida P, Altman DG, et al. PRISMA harms checklist: improving harms reporting in systematic reviews. Bmj. 2016;352:i157.

4. Deposition of Linda Loretz 562:14-563:6 (October 1, 2018).

5. Deposition of Joshua Muscat 408:21-410:20 (September 25, 2018).

6. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009) [Web]. Oxford, UK: Nuffield Department of Primary Health Care; 2009 [cited 2018 Nov 15]. Available from: http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/.

7. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557-60.

8. Berlin JA, Santanna J, Schmid CH, Szczech LA, Feldman HI. Individual patient- versus group-level data meta-regressions for the investigation of treatment effect modifiers: ecological bias rears its ugly head. Statistics in medicine. 2002;21(3):371-87.

9. da Costa BR, Jüni P. Systematic reviews and meta-analyses of randomized trials: principles and pitfalls. European Heart Journal. 2014;35(47):3336-45.

10. Terry KL, Karageorgi S, Shvetsov YB, Merritt MA, Lurie G, Thompson PJ, et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. Cancer Prev Res. 2013;6(8):811-21.

11. Ioannidis JPA. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2009;181(8):488-93.

12. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. Journal of clinical epidemiology. 2009;62(10):1013-20.

13. Huncharek M, Muscat J, Onitilo A, Kupelnick B. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: A meta-analysis of nine observational studies. EurJ Cancer Prev. 2007;16(5):422-9.

14. Gertig DM, Hunter DJ, Cramer DW, Colditz GA, Speizer FE, Willett WC, et al. Prospective study of talc use and ovarian cancer. J Natl Cancer Inst. 2000;92(3):249-52.

15. Ray WA. Evaluating Medication Effects Outside of Clinical Trials: New-User Designs. AM J EPIDEMIOL. 2003;158(9):915-20.

16. Hannan MT. Is it a risk factor or confounder? A discussion of selected analytic methods using education as an example. Arthritis & Rheumatism. 1996;9(5):413-8.

17. Houghton SC, Reeves KW, Hankinson SE, Crawford L, Lane D, Wactawski-Wende J, et al. Perineal powder use and risk of ovarian cancer. J Natl Cancer Inst. 2014;106(9).

18. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. The American Statistician. 2016;70(2):129-33.

19. Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. British Medical Journal (Clinical research ed). 1986;292(6522):746-50.

20. CDC. United States Cancer Statistics: 1999-2014 Incidence and Mortality Web-based Report2017 March 4 2018 [cited 2018 March 24]. Available from: www.cdc.gov/uscs.

21. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA: A Cancer Journal for Clinicians. 2017;67(1):7-30.

22. Rohl AN, Langer AM, Selikoff IJ, Tordini A, Klimentidis R, Bowes DR, et al. Consumer talcums and powders: mineral and chemical characterization. Journal of toxicology and environmental health. 1976;2(2):255-84.

23. Crowley, M. Report of Michael M. Crowley, PhD. Regarding the Fragrance Chemical Constituents in Johnson & Johnson Talcum Powder Products (November 12, 2018).

24. Rohl AN. Asbestos in talc. Environmental health perspectives. 1974;9:129-32.

25. Paoletti L, Caiazza S, Donelli G, Pocchiari F. Evaluation by electron microscopy techniques of asbestos contamination in industrial, cosmetic, and pharmaceutical talcs. Regulatory toxicology and pharmacology : RTP. 1984;4(3):222-35.

26. Blount AM. Amphibole content of cosmetic and pharmaceutical talcs. Environmental health perspectives. 1991;94:225-30.

27. Deposition of Alice M. Blount, 105:21-106:6 (April 13, 2018).

28. Food and Drug Administration; 2018 [updated March 12 2018; cited 2018 November 15]. Available from: https://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm293184.htm.

29. JNJ000637879-JNJ000637881.

30. Longo, et. al. Analysis of Johnson & Johnso*n* Baby Powder & Valiant Shower to Shower Talc Products for Amphibole (Tremolite) Asbestos (August 2, 2017).

31. Longo, et al. MAS Project # 14-1683 Johnson's Baby Powder Sample Set (April 28, 2017).

32. Longo, et al. TEM Analysis of Historical 1978 Johnson's Baby Powder Sample for Asbestos (February 16, 2018).

33. Deposition of John Hopkins, Exhibit 28 (November 5, 2018).

34. Longo, et al. *In re: Talcum Power Prod. Liab. Litig*., MDL No. 2738 (Nov. 14, 2018).

35. Deposition of Julie Pier, Exhibit 47 (September 13, 2018).

36. International Agency for Research in Cancer Monographs on the Evaluation of Carcinogenic Risks to Humans: Volume 100C Arsenic, Metals, Fibers and Dusts (2012)

37. Straif K, Benbrahim-Tallaa L, Baan R, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens. Part C: metals, arsenic, dusts, and fibres. The Lancet Oncology. 2009;10(5):453-4.

38. World Health Organization. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Carbon Black, Titanium Dioxide, and Talc Lyon 2010

39. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. J EXPOS ANAL ENVIRON EPIDEMIOL. 1995;5(2):181-95.

40. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: A meta-analysis of 11, 933 subjects from sixteen observational studies. Anticancer Res. 2003;23(2 C):1955-60.

41. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. EurJ Cancer Prev. 2018; 27(3): 248-257.

42. Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. Epidemiology. 2018;29(1):41-9.

43. Lane PW, Higgins JP, Anagnostelis B, Anzures-Cabrera J, Baker NF, Cappelleri JC, et al. Methodological quality of meta-analyses: matched-pairs comparison over time and between industry-sponsored and academic-sponsored reports. Research synthesis methods. 2013;4(4):342-50.

44. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. Bmj. 1997;315(7114):980-8.

45. Kim S, Ko Y, Lee HJ, Lim JE. Menopausal hormone therapy and the risk of breast cancer by histological type and race: a meta-analysis of randomized controlled trials and cohort studies. Breast cancer research and treatment. 2018;170(3):667-75.

46. Hamra GB, Guha N, Cohen A, Laden F, Raaschou-Nielsen O, Samet JM, et al. Outdoor particulate matter exposure and lung cancer: a systematic review and meta-analysis. Environmental health perspectives. 2014;122(9):906-11.

47. Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, et al. Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA. 2012;307(7):713-21.

48. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles county. INT J CANCER. 2009;124(6):1409-15.

49. Fletcher NM, Memaj I, Saed GM. Talcum Powder Enhances Oxidative Stress in Ovarian Cancer Cells, Reproductive Sciences. 2018;25(1_suppl):1A-54A.

50. Ioannidis JP. Exposure-wide epidemiology: revisiting Bradford Hill. Statistics in medicine. 2016;35(11):1749-62.

51. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case-control study. British journal of cancer. 1989;60(4):592-8.

52. Schildkraut JM, Abbott SE, Alberg AJ, Bandera EV, Barnholtz-Sloan JS, Bondy ML, et al. Association between Body Powder Use and Ovarian Cancer: the African American Cancer Epidemiology Study (AACES). Cancer Epidemiology Biomarkers & Prevention. 2016.

53. Wu AH, Pearce CL, Tseng CC, Pike MC. African Americans and hispanics remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. Cancer Epidemiol Biomarkers Prev. 2015;24(7):1094-100.
54. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer a retrospective case-control study in two us states. Epidemiology. 2016;27(3):334-46.
55. Gates MA, Tworoger SS, Terry KL, Titus-Ernstoff L, Rosner B, De Vivo I, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2436-44.
56. Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. CANCER. 1997;79(12):2396-401.
57. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. INT J CANCER. 1999;81(3):351-6.
58. Whittemore AS, Wu ML, Paffenbarger RS, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer: II. Exposures to talcum powder, tobacco, alcohol, and coffee. AM J EPIDEMIOL. 1988;128(6):1228-40.
59. Mills PK, Riordan DG, Cress RD, Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the central valley of California. INT J CANCER. 2004;112(3):458-64.
60. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, Wicklund KG, Rossing MA. Genital powder exposure and the risk of epithelial ovarian cancer. Cancer Causes Control. 2011;22(5):737-42.
61. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. J Natl Cancer Inst. 1999;91(17):1459-67.
62. Green A, Purdie D, Bain C, Siskind V, Russell P, Quinn M, et al. Tubal sterilisation, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. Int J Cancer. 1997;71(6):948-51.
63. JNJ000460665-JNJ000460673.
64. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. AM J OBSTET GYNECOL. 1996;174(5):1507-10.
65. Henderson WJ, Joslin CA, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. The Journal of obstetrics and gynaecology of the British Commonwealth. 1971;78(3):266-72.
66. Cramer DW, Welch WR, Berkowitz RS, Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. Obstet Gynecol. 2007;110(2 II):498-501.
67. Wehner AP, Weller RE, Lepel EA. On talc translocation from the vagina to the oviducts and beyond. Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 1986;24(4):329-38.
68. Sjosten AC, Ellis H, Edelstam GA. Retrograde migration of glove powder in the human female genital tract. Human reproduction (Oxford, England). 2004;19(4):991-5.
69. FDA response to Citizen's Petition (2014), JNJ000489048- JNJ000489054.

70. Longo, et al. Below the Waist Application of Johnson & Johnson Baby Powder (September 2017).
71. Buz'Zard AR, Lau BHS. Pycnogenol® reduces talc-induced neoplastic transformation in human ovarian cell cultures. Phytother Res. 2007;21(6):579-86.
72. Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2005;14(5):1125-31.
73. Langseth H, Hankinson SE, Siemiatycki J, Weiderpasse E. Perineal use of talc and risk of ovarian cancer. J Epidemiol Community Health. 2008;62(4):358-60.
74. Muscat JE, Huncharek MS. Perineal Talc Use and Ovarian Cancer: A Critical Review. European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP). 2008;17(2):139-46.
75. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc. A case-control study. CANCER. 1982;50(2):372-6.
76. Hartge P, Hoover R, Lesher LP, McGowan L. Talc and Ovarian Cancer. JAMA. 1983;250(14):1844.
77. Harlow BL, Weiss NS. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol. 1989;130(2):390-4.
78. Chen Y, Wu PC, Lang JH, Ge WJ, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol. 1992;21(1):23-9.
79. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol. 1992;80(1):19-26.
80. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. Gynecol Oncol. 1992;45(1):20-5.
81. Tzonou A, Polychronopoulou A, Hsieh CC, Trichopoulos D, Rebelakos A, Karakatsani A. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. INT J CANCER. 1993;55(3):408-10.
82. Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case-control study. Survey of Women's Health Study Group. Int J Cancer. 1995;62(6):678-84.
83. Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker JG. Human menopausal gonadotropin and the risk of epithelial ovarian cancer *. FERTIL STERIL. 1996;65(1):13-8.
84. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. AM J EPIDEMIOL. 1997;145(5):459-65.
85. Godard B, Foulkes WD, Provencher D, Brunet J-S, Tonin PN, Mes-Masson A-M, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: A case-control study. AM J OBSTET GYNECOL. 1998;179(2):403-10.

86. Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: A case- control study. Obstet Gynecol. 1999;93(3):372-6.
87. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. Epidemiology. 2000;11(2):111-7.
88. Langseth H, Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. Scandinavian journal of work, environment & health. 2004;30(5):356-61.
89. Merritt MA, Green AC, Nagle CM, Webb PM, Bowtell D, Chenevix-Trench G, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. INT J CANCER. 2008;122(1):170-6.
90. Moorman PG, Palmieri RT, Akushevich L, Berchuck A, Schildkraut JM. Ovarian Cancer Risk Factors in African-American and White Women. AM J EPIDEMIOL. 2009;170(5):598-606.
91. Kurta ML, Moysich KB, Weissfeld JL, Youk AO, Bunker CH, Edwards RP, et al. Use of fertility drugs and risk of ovarian cancer: Results from a U.S.-based case-control study. Cancer Epidemiol Biomarkers Prev. 2012;21(8):1282-92.
92. Gates MA, Rosner BA, Hecht JL, Tworoger SS. Risk factors for epithelial ovarian cancer by histologic subtype. Am J Epidemiol. 2010;171(1):45-53.
93. Gonzalez NL, O'Brien KM, D'Aloisio AA, Sandler DP, Weinberg CR. Douching, talc use, and risk of ovarian cancer. Epidemiology. 2016;27(6):797-802.
94. Henderson WJ, Hamilton TC, Griffiths K. Talc in normal and malignant ovarian tissue. Lancet. 1979;1(8114):499.
95. Wehner AP, Hall AS, Weller RE, Lepel EA, Schirmer RE. Do particles translocate from the vagina to the oviducts and beyond? Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association. 1985;23(3):367-72.
96. Hartge P, Stewart P. Occupation and ovarian cancer: A case-control study in the Washington, DC, metropolitan area, 1978–1981. J Occup Med. 1994;36(8):924-7.
97. Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. REGUL TOXICOL PHARMACOL. 1995;21(2):242-3.
98. Cramer DW, Xu H. Epidemiologic evidence for uterine growth factors in the pathogenesis of ovarian cancer. Ann Epidemiol. 1995;5(4):310-4.
99. Heller DS, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. AM J IND MED. 1996;29(5):435-9.
100. Rosenblatt KA, Mathews WA, Daling JR, Voigt LF, Malone K. Characteristics of women who use perineal powders. Obstet Gynecol. 1998;92(5):753-6.
101. Muscat J, Huncharek M, Cramer DW.Talc and anti-MUC1 antibodies.Cancer Epidemiol Biomarkers Prev. 2005 Nov;14(11 Pt 1):2679; author reply.
102. Keskın N, Teksen YA, Ongun EG, Özay Y, Saygılı H. Does long-term talc exposure have a carcinogenic effect on the female genital system of rats? An experimental pilot study. Arch Gynecol Obstet. 2009;280(6):925-31.

103. Karageorgi S, Gates MA, Hankinson SE, De Vivo I. Perineal use of talcum powder and endometrial cancer risk. Cancer Epidemiol Biomarkers Prev. 2010;19(5):1269-75.
104. Gordon RE, Fitzgerald S, Millette J. Asbestos in commercial cosmetic talcum powder as a cause of mesothelioma in women. International journal of occupational and environmental health. 2014;20(4):318-32.
105. Pierce JS, Riordan AS, Miller EW, Gaffney SH, Hollins DM. Evaluation of the presence of asbestos in cosmetic talcum products. Inhalation toxicology. 2017;29(10):443-56.
106. Nicole M Fletcher, Ira Memaj, Ghassan M Saed. Talcum Powder Enhances Cancer Antigen 125 levels in Ovarian Cancer Cells, Society for Reproductive Investigation 65th Annual Scientific Meeting, LB-044. 2018.
107. Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K. Effects of talc on the rat ovary. British journal of experimental pathology. 1984;65(1):101-6.
108. NTP Toxicology and Carcinogenesis Studies of Talc (CAS No. 14807-96-6)(Non-Asbestiform) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). National Toxicology Program technical report series. 1993;421:1-287.
109. Shukla A, MacPherson MB, Hillegass J, Ramos-Nino ME, Alexeeva V, Vacek PM, et al. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. American journal of respiratory cell and molecular biology. 2009;41(1):114-23.
110. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. PLOS Medicine. 2009;6(7):e1000100.
111. Berretta M, Micek A, Lafranconi A, Rossetti S, Di Francia R, De Paoli P, et al. Coffee consumption is not associated with ovarian cancer risk: a dose-response meta-analysis of prospective cohort studies. Oncotarget. 2018;9(29):20807-15.
112. Ong JS, Hwang LD, Cuellar-Partida G, Martin NG, Chenevix-Trench G, Quinn MCJ, et al. Assessment of moderate coffee consumption and risk of epithelial ovarian cancer: a Mendelian randomization study. Int J Epidemiol. 2018;47(2):450-9.
113. Cramer DW, Piver MS. Perineal talc exposure and subsequent epithelial ovarian cancer: A case-control study [4] (multiple letters). Obstet Gynecol. 1999;94(1):160-1.
114. Giovannucci E, Stampfer MJ, Colditz GA, Manson JE, Rosner BA, Longnecker MP, et al. Recall and selection bias in reporting past alcohol consumption among breast cancer cases. Cancer Causes & Control. 1993;4(5):441-8.
115. Rice MS, Murphy MA, Tworoger SS. Tubal ligation, hysterectomy and ovarian cancer: A meta-analysis. Journal of ovarian research. 2012;5(1):13-.
116. IMERYS137677.
117. Zazenski R, Ashton WH, Briggs D, Chudkowski M, Kelse JW, MacEachern L, et al. Talc: occurrence, characterization, and consumer applications. Regulatory toxicology and pharmacology : RTP. 1995;21(2):218-29.

118. Klaassen CD, Watkins JB. Casarett & Doull's Essentials of Toxicology, Third Edition. Leikauf G.D., editor. New York: McGraw-Hill Education; 2015.
119. Suzuki Y, Kohyama N. Translocation of inhaled asbestos fibers from the lung to other tissues. Am J Ind Med. 1991;19(6):701-4.
120. Bunderson-Schelvan M, Pfau JC, Crouch R, Holian A. Nonpulmonary outcomes of asbestos exposure. Journal of toxicology and environmental health Part B, Critical reviews. 2011;14(1-4):122-52.
121. Kelly MG, Pejovic T, Nezhat FR. What is the relationship between endometriosis and epithelial ovarian cancer? CME J Gynecol Oncol. 2003;8(1):41-7.
122. Rasmussen CB, Kjaer SK, Albieri V, Bandera EV, Doherty JA, Hogdall E, et al. Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. Am J Epidemiol. 2017;185(1):8-20.
123. Trabert B, Pinto L, Hartge P, Kemp T, Black A, Sherman ME, et al. Pre-diagnostic serum levels of inflammation markers and risk of ovarian cancer in the Prostate, Lung, Colorectal and Ovarian Cancer (PLCO) Screening Trial. Gynecol Oncol. 2014;135(2):297-304.
124. Ghassan M Saed,.Robert T Moriss and Nicole Fletecher. New Insights into the Pathogenesis of Ovarian Cancer: Oxidative Stress. 2018 October 24 2018. Available from https://www.intechopen.com/books/ovarian-cancer-from-pathogenesis-to-treatment
125. Saed GM, Diamond MP, Fletcher NM. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. Gynecol Oncol. 2017;145(3):595-602.
126. Oberdorster G. The NTP Talc Inhalation Study: A Critical Appraisal Focused on Lung Particle Overload. REGUL TOXICOL PHARMACOL. 1995;21(2):233-41.
127. Camargo MC, Stayner LT, Straif K, Reina M, Al-Alem U, Demers PA, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. Environmental health perspectives. 2011;119(9):1211-7.
128. WHO IARC. Preamble. [Web]. Lyon, France: IARC; 2006 [updated September 4 2015; cited 2018 Nov 10]. Available from: https://monographs.iarc.fr/preamble-to-the-iarc-monographs-amended-january-2006/.
129. Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Cogliano V. Carcinogenicity of carbon black, titanium dioxide, and talc. The Lancet Oncology.7(4):295-6.
130. Fiume M, Ivan B, Wilma FB, Donald VB, Ronald AH, Curtis DK, et al. Safety Assessment of Talc as Used in Cosmetics. International Journal of Toxicology. 2015;34(1_suppl):66S-129S
131. Reports of the Surgeon General. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2006.
132. Rothwell PM, Cook NR, Gaziano JM, Price JF, Belch JFF, Roncaglioni MC, et al. Effects of aspirin on risks of vascular events and cancer according to bodyweight and dose: analysis of individual patient data from randomised trials. Lancet. 2018;392(10145):387-99.

133. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, et al. Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. BMJ : British Medical Journal. 2014;349.

Criterion	Harlow et al 1992[1]	Gross and Berg et al 1995[2]	Cramer et al 1999[3]	Huncharek et al 2003[4]	Langseth et al 2007[5]	Terry et al 2013 #[6]	Berge et al 2018[7]	Penninkilampi and Eslick 2018.[8]	Huncharek et al 2007 [9]*
A priori design	UA	Y	N	UA	UA	Y	Y	Y	UA
Duplicate study selection & extraction	N	N	N	Y	N	NA	Y	Y	Y
Comprehensive search	N	N	N	UA	N	NA	Y	Y	N
Status of publication used as criterion	UA	N	UA	Y	UA	NA	Y	N	Y
List of included & excluded studies	N	N	N	N	N	Y	Y	Y	N
Characteristics of studies provided	N	Y	N	N	N	Y	Y	Y	Y
Scientific quality of studies addressed	N	UA	N	N	Y	Y	Y	Y	N
Scientific quality of studies used in formulating conclusions	N	Y	UA	N	Y	Y	Y	Y	N
Methods of combining studies appropriate	N	Y	Y	Y	Y	Y	Y	Y	N
Likelihood of publication bias addressed	N	N	N	N	N	NA	Y	Y	N
Conflict of interest included	Y	Y	Y	UA@	Y	Y	Y	Y	UA@

Table 1. AMSTAR (Assessing the Methodologic Quality of Systematic Reviews) Rating of Systematic Reviews and/or Meta-analysis of Genital Talc use and Ovarian Cancer

*Meta-analysis by Huncharek et al in 2007 et al evaluated only talc on contraceptive diaphragms
Terry et al 2013 conducted an individual participant data pooled analysis so several items for systematic review NA
@ Incomplete financial disclosures of role of sponsor in meta-analysis
Y= Yes N= No; NA= Not applicable; UA : Unable to answer

1. Harlow BL, Cramer DW, Bell DA, et al. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992;80(1):19-26.
2. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *J EXPOS ANAL ENVIRON EPIDEMIOL* 1995;5(2):181-95.
3. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. *INT J CANCER* 1999;81(3):351-56.
4. Huncharek M, Geschwind JF, Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: A meta-analysis of 11, 933 subjects from sixteen observational studies. *Anticancer Res* 2003;23(2 C):1955-60.
5. Langseth H, Hankinson SE, Siemiatycki J, et al. Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health* 2008;62(4):358-60. doi: 10.1136/jech.2006.047894
6. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res* 2013;6(8):811-21. doi: 10.1158/1940-6207.CAPR-13-0037
7. Berge W, Mundt K, Luu H, Boffetta P. Genital use of talc and risk of ovarian cancer: a meta-analysis. EurJ Cancer Prev. 2018; 27(3): 248-257
8. Penninkilampi R, Eslick GD. Perineal Talc Use and Ovarian Cancer: A Systematic Review and Meta-Analysis. *Epidemiology* 2018;29(1):41-49. doi: 10.1097/ede.0000000000000745 [published Online First: 2017/09/02]
9. Huncharek M, Muscat J, Onitilo A, et al. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: A meta-analysis of nine observational studies. *EurJ Cancer Prev* 2007;16(5):422-29. doi: 10.1097/01.cej.0000236257.03394.4a

Additional Materials and Data Considered

1. Adler RH, Rappole BW. Recurrent malignant pleural effusions and talc powder aerosol treatment. Surgery. 1967;62(6):1000-6.

2. Adler RH, Sayek I. Treatment of malignant pleural effusion: a method using tube thoracostomy and talc. The Annals of thoracic surgery. 1976;22(1):8-15.

3. Ainsworth S. Not safe for babies' bottom? The practising midwife. 2009;12(4):42.

4. Baker TR, Piver MS. Etiology, biology, and epidemiology of ovarian cancer. Semin Surg Oncol. 1994;10(4):242-8.

5. Balkwill, Mantovani. Inflammation and Cancer: Back to Vircvchow? Lancet. 2011; 357(9255):539-45.

6. Barbetakis N, Asteriou C, Papadopoulou F, Samanidis G, Paliouras D, Kleontas A, et al. Early and late morbidity and mortality and life expectancy following thoracoscopic talc insufflation for control of malignant pleural effusions: A review of 400 cases. J Cardiothoracic Surg. 2010;5(1).

7. Begg, March. Cause and Association: missing the forest for the trees. American Journal of Public Health (AJPH). 2018; Vol. 108, No. 5.

8. Bernal LS, Ramos CLM. Risk factors for ovary carcinoma. REV INST NAC CANCEROL. 1996;42(4):213-20.

9. Berge, Wera, Kenneth Mundt, Hung Luu, and Paolo Boffetta. 2017. “Genital Use of Talc and Risk of Ovarian Cancer: A Meta-Analysis.” *European Journal of Cancer Prevention*, January, 1. https://doi.org/10.1097/CEJ.0000000000000340.

10. Bielsa S, Hernández P, Rodriguez-Panadero F, Taberner T, Salud A, Porcel JM. Tumor type influences the effectiveness of pleurodesis in malignant effusions. Lung. 2011;189(2):151-5.

11. Boente MP, Godwin AK, Hogan WM. Screening, imaging, and early diagnosis of ovarian cancer. CLIN OBSTET GYNECOL. 1994;37(2):377-91.

12. Bondoc AYP, Bach PB, Sklarin NT, Vander Els NJ. Arterial Desaturation Syndrome Following Pleurodesis with Talc Slurry: Incidence, Clinical Features, and Outcome. Cancer Invest. 2003;21(6):848-54.

13. Bronner GM, Baas P, Beijnen JH. Pleurodesis in malignant pleural effusions. NED TIJDSCHR GENEESKD. 1997;141(38):1810-4.

14. Bulbulyan MA, Ilychova SA, Zahm SH, Astashevsky SV, Zaridze DG. Cancer mortality among women in the Russian printing industry. AM J IND MED. 1999;36(1):166-71.

15. Carr CJ. Talc: Consumer uses and health perspectives. Proceedings of a Workshop. Bethesda, Maryland, January 31-February 1, 1994 . Regulatory Toxicology and Pharmacology: RTP. 1995; 21(2):211-60.

16. Chang, Tu, Chen, Yang. Occupational exposure to talc increases the risk of lung cancer: a meta-analysis of occupational cohort studies. Canadian Respiratory Journal. 2017; 2017:1270608.

17. Chi DS, Abu-Rustum NR, Sonoda Y, Chen SWW, Flores RM, Downey R, et al. The benefit of video-assisted thoracoscopic surgery before planned abdominal exploration in

patients with suspected advanced ovarian cancer and moderate to large pleural effusions. Gynecol Oncol. 2004;94(2):307-11.
18. Cook LS. No significant association was found between perinea! talcum powder use and epithelial ovarian cancer. Evid-based Obstet Gynecol. 2000;2(2):53-4.
19. Coussens, L.M. and and Z Werb. Inflammation and cancer. Nature. 2002; 420(6917):860-867.
20. Cralley L, M Key, D Groth, W Lainhart, R Ligo. Fibrous and mineral content of cosmetic talcum products. American Industrial Hygiene Association Journal. 1968; 29(4):350-354.
21. Cramer DW, Finn OJ. Epidemiologic perspective on immune-surveillance in cancer. Curr Opin Immunol. 2011;23(2):265-71.
22. Cramer DW. The Epidemiology of Endometrial and Ovarian Cancer. Hematol Oncol Clin North Am. 2012;26(1):1-12.
23. Critchley LA, Au HK, Yim AP. Reexpansion pulmonary edema occurring after thoracoscopic drainage of a pleural effusion. Journal of clinical anesthesia. 1996;8(7):591-4.
24. Crusz, Balkwill . Inflammation and cancer: advances and new agents. Nature reviews. Clinical Oncology. 2015; 12(10):584-96.
25. Curie P, Sussmann M, Treisser A, Renaud R. Epidemiologic factors in ovarian carcinoma. REV FR GYNECOL OBSTET. 1985;80(6):379-82.
26. Current Intelligence Bulletin 62(Rev/4/2011) – Asbestos fibers and other elongate mineral particles: state of the science and roadmap for research. National Institute for Occupational Safety and Health (NIOSH) DHSS. (NIOSH) publication No. 2011-159.
27. Dalley VM. The role of radiotherapy and chemotherapy in the treatment of cancer of the ovary. Int J Radiat Oncol Biol Phys. 1982;8(2):251-5.
28. Daly M, Obrams GI. Epidemiology and risk assessment for ovarian cancer. Semin Oncol. 1998;25(3):255-64.
29. Dement, Schuler, Zumwalde. “fiber exposure during use of baby powders”. National Institute for Occupational Safety and Health, IWS. 1972; 36-6:1-13.
30. Dial J, Marzusch K. Ovarian surface epithelium and human ovarian cancer. Gynecol Obstet Invest. 1993;35(3):129-35.
31. Dietl J, Buchholz F, Stoll P. The ovarian surface epithelium and its histogenetic relation to ovarian carcinoma. GEBURTSHILFE FRAUENHEILKD. 1986;46(9):561-6.
32. Eberl, George, May Jr., Henderson. Comparative evaluation of the effects of talcum and new absorbable substitute of surgical gloves. The American Journal of Surgery. 1948; Vol. 75, Issue 3, Pgs. 493-497.
33. Egli G, M. Newton. The transport of carbon particles in the human female reproductive tract, Fertility and Sterility 1961;12(April):151-55.
34. Elmasry K, Gayther SA. Ovarian cancer aetiology: Facts and fiction. J Fam Plann Reprod Health Care. 2006;32(2):82-6.

35. Eltabbakh GH, Piver MS, Natarajan N, Mettlin CJ. Epidemiologic differences between women with extraovarian primary peritoneal carcinoma and women with epithelial ovarian cancer. Obstet Gynecol. 1998;91(2):254-9.
36. Erickson KV, Yost M, Bynoe R, Almond C, Nottingham J. Primary treatment of malignant pleural effusions: video-assisted thoracoscopic surgery poudrage versus tube thoracostomy. The American surgeon. 2002;68(11):955-9; discussion 9-60.
37. Fedak, Kristen M., Autumn Bernal, Zachary A. Capshaw, and Sherilyn Gross. 2015. "Applying the Bradford Hill Criteria in the 21st Century: How Data Integration Has Changed Causal Inference in Molecular Epidemiology." *Emerging Themes in Epidemiology* 12 (14). https://doi.org/10.1186/s12982-015-0037-4.
38. Federal Judicial Center and National Research Council of the National Academies (2011). Reference Manual on Scientific Evidence, Third Edition. Washington, D.C., The National Academies Press.
39. Fernandes, Cobucci, Jatoba, Fernandes, deAzevedo, De Arujo.The role of the mediators of inflammation in cancer development. Pathology Oncology Research: POR. 2015; 21(3):527-34.
40. Fletcher N, J Belotte, M Saed, Memaj, M Diamond, R Morris, G Saed . Talcum Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. Fee Radical Bilogy and Medicine. 2016; 102:122-132.
41. Filosso PL, Sandri A, Felletti G, Ruffini E, Lausi PO, Oliaro A. Preliminary results of a new small-bore percutaneous pleural catheter used for treatment of malignant pleural effusions in ECOG PS 3-4 patients. Eur J Surg Oncol. 2011;37(12):1093-8.
42. Folkins A, E Jarboe, J Hecht, M Muto and C Crum (2018). "Chapter 24 – Assessing pelvic epithelial cancer risk and intercepting early malignancy." In Diagnostic Gynecologic and Obstetric Pathology (Third Edition), 844-64. Philadelphia: Content Repository Only! https://doi.org/10.1016/B978-0-323-44732-4.00024-8.
43. Galea, Rogers. Moving beyond the cause constraint: a public health of consequence. The American Journal of Public Health. Vol. 108, No.5. 2018; Editorial 602-603.
44. Glyone S. Two cases of squamous carcinoma of the lung occurring in asbestosis. Tubercle. 1935; (17)1:5-10.
45. Gori GB. Session II: Introduction-ovarian exposure concerns. REGUL TOXICOL PHARMACOL. 1995;21(2):252-3.
46. Goff BA, Mueller PR, Muntz HG, Rice LW. Small chest-tube drainage followed by bleomycin sclerosis for malignant pleural effusions. Obstet Gynecol. 1993;81(6):993-6.
47. Graham, Jenkins. Value of modified starch as substitute for talc. Lancet. 1952; 1(6708):590-1.
48. Griffiths K, Chandler JA, Henderson WJ, Joslin CAF. Ovarian cancer: some new analytical approaches. Postgrad Med J. 1973;49(568):69-72.
49. Grivennikov, Greten, Karin M. Immunity, inflammation and cancer. Cell. 2010; 140(6):883-99.

50. Gross JL, Disanzio TG, Younes RN, Haddad FJ, Da Silva RA, Avertano ABM. Do concomitant ascites influence the effectiveness of palliative surgical management of pleural effusion in patients with malignancies? World J Surg. 2009;33(2):266-71.
51. Harper A, G Saed. Talc induces a pro-oxidant state in normal and ovarian cancer cells through gene point mutations in key redox enzymes - Abstract, Society of Gynecologic Oncology, 2018, *in press*.
52. Hartge PA. A Review of Perineal Talc Exposure and Risk of Ovarian Cancer. REGUL TOXICOL PHARMACOL. 1995;21(2):254-60.
53. Harter P, Du Bois A. Does tubal sterilization protect against ovarian cancer? Gynakol Prax. 2003;27(3):455-8.
54. Herbst AL. The epidemiology of ovarian carcinoma and the current status of tumor markers to detect disease. AM J OBSTET GYNECOL. 1994;170(4):1099-107.
55. Hernan. The C-word: scientific euphemisms do not improve causal inference from observational data. The American Journal of Public Health (AJPH). 2018; Vol. 108. No. 5:616-619.
56. Horiuchi A, Konishi I. Prevention of ovarian cancer development. Nippon Rinsho. 2004;62 Suppl 10:597-600.
57. Horn D, Dequanter D, Lothaire P. Palliative treatment of malignant pleural effusions. Acta Chir Belg. 2010;110(1):32-4.
58. Huncharek M, Muscat J. Perineal talc use and ovarian cancer risk: A case study of scientific standards in environmental epidemiology. EurJ Cancer Prev. 2011;20(6):501-7.
59. IARC (International Agency for Research on Cancer) (1987) Talc. IARC monographs on evaluation of carcinogenic risk of chemicals to humans, Vol. 42, IARC, Lyon, France, 185-224.
60. IARC (International Agency for Research on Cancer) (2010) Carbon black, titanium dioxide, and talc, Vol. 93, IARC, Lyon, France.
61. IARC (International Agency for Research on Cancer) (2012) Talc. Arsenic, Metals Fibres, and Dusts: A review of human carcinogens, Vol. 100C, IARC, Lyon, France.
62. Institute of Medicine; National Academies of Sciences, Engineering, and Medicine (2016). *Ovarian Cancers: Evolving Paradigms in Research and Care*
63. Hunn J, Rodriguez GC. Ovarian cancer: Etiology, risk factors, and epidemiology. CLIN OBSTET GYNECOL. 2012;55(1):3-23.
64. Jordan SJ, Purdie DM, Whiteman DC, Webb PM. Risk factors for epithelial ovarian cancer. Cancer Forum. 2003;27(3):148-51.
65. Kasper CS, Chandler PJ, Jr. Possible morbidity in women from talc on condoms. JAMA. 1995;273(11):846-7.
66. Kennedy L, Rusch VW, Strange C, Ginsberg RJ, Sahn SA. Pleurodesis using talc slurry. CHEST. 1994;106(2):342-6.
67. Kiraly O, Gong G, Olipitz W, Muthupalani S, Engelward BP. Inflammation-induced cell proliferation potentiates DNA damage-induced mutations in vivo. PLoS genectics. 2015; 11(2): e1004901.

68. Kolschmann S, Ballin A, Gillissen A. Clinical efficacy and safety of thoracoscopic talc pleurodesis in malignant pleural effusions. CHEST. 2005;128(3):1431-5.

69. Kupryjańczyk J. Adenomatoid tumour of the ovary and uterus in the same patient. Zentralbl Allg Pathol. 1989;135(5):437-44.

70. Ladjimi S, M'Raihi L, Djemel A, Mathlouthi A, Ben Ayed F, Zegaya M. [Results of talc administration using thoracoscopy in neoplastic pleurisies. Apropos of 218 cases]. Revue des maladies respiratoires. 1989;6(2):147-50.

71. Langseth H, Andersen A. Cancer incidence among women in the Norwegian pulp and paper industry. AM J IND MED. 1999;36(1):108-13.

72. Lauchlan SC. The secondary mullerian system revisited. International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists. 1994;13(1):73-9.

73. La Vecchia C. Epidemiology of ovarian cancer: A summary review. EurJ Cancer Prev. 2001;10(2):125-9.

74. Levin. "Baby powder battles: Johnson & Johnson internal documents reveal asbestos worries". https//www.fairwarning.org/2018/01/talc-documents-reveal/.

75. Lockey. Nonasbestos fibrous minerals. Clinics in chest medicine. 1981; 2(2):203-18.

76. Lombardi G, Nicoletto MO, Gusella M, Fiduccia P, Dalla Palma M, Zuin A, et al. Intrapleural paclitaxel for malignant pleural effusion from ovarian and breast cancer: A phase II study with pharmacokinetic analysis. Cancer Chemother Pharmacol. 2012;69(3):781-7.

77. Longo D, Young R. COSMETIC TALC AND OVARIAN CANCER. Lancet. 1979;314(8150):1011-2.

78. Lowe KA, Shah C, Wallace E, Anderson G, Paley P, McIntosh M, et al. Effects of personal characteristics on serum CA125, mesothelin, and HE4 levels in healthy postmenopausal women at high-risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2008;17(9):2480-7.

79. Lundin, Dossus, Clendenen, Krogh, Grankvist, Wulff, Sieri, Arlsan, Lenner, Berrino, Hallmans, Zeleniuch-Jacquotte, Toniolo, Lukanova. C-reactive protein and ovarian cancer: a prospective study nested in three cohorts (Sweden, USA, Italy). Caner Causes & Control: CCC. 2009; Vol. 20, Issue 7, PP 1151-1159.

80. Lumachi F, Mazza F, Ermani M, Chiara GB, Basso SMM. Talc pleurodesis as surgical palliation of patients with malignant pleural effusion. Analysis of factors affecting survival. Anticancer Res. 2012;32(11):5071-4.

81. Mad'Ar R, Straka S, Baška T. Is ovarian cancer associated with talcum powder? Hygiena. 2002;47(4):239-42.

82. Mager HJ, Maesen B, Verzijlbergen F, Schramel F. Distribution of talc suspension during treatment of malignant pleural effusion with talc pleurodesis. Lung cancer (Amsterdam, Netherlands). 2002;36(1):77-81.

83. Malden LT, Tattersall MH. Malignant effusions. QJM. 1986;58(3-4):221-39.

84. Mallen, Townsend, Tworoger. Risk factors for ovarian carcinoma. Hematology/Oncology Clinics of North America. 2018; 32(6):891-902.
85. Markman M, Muggia FM. Intracavitary chemotherapy. Crit Rev Oncol Hematol. 1985;3(3):205-33.
86. Mayer D, C Kasper, P Chandler (1995). To the Editor: Talc and Condoms and reply, JAMA 274(16):1269.
87. McLemore MR, Miaskowski C, Aouizerat BE, Chen LM, Dodd MJ. Epidemiological and genetic factors associated with ovarian cancer. Cancer Nurs. 2009;32(4):281-8.
88. Medford ARL, Maskell NA. A national survey of oncologist and chest physicians' attitudes towards empirical anti-oestrogen therapy, early pleurodesis and preference of sclerosing agents in malignant breast and ovarian pleural disease [1]. Palliative Med. 2005;19(5):430-1.
89. Meisler JG. Toward optimal health: The experts discuss ovarian cancer. J Women's Health Gender Med. 2000;9(7):705-10.
90. Møller P, P Danielsen, K Jantzen, M Roursgaard & S Loft. Oxidatively damaged DNA in animals exposed to particles, Critical Reviews in Toxicology, 2013;43:2, 96-118
91. Møller P, N Jacobsen, J Folkmann, P Danielsen, L Mikkelsen, J Hemmingsen, L Vesterdal, L Forchhammer, H Wallin & S Loft. Role of oxidative damage in toxicity of particulates, Free Radical Research, 2010;44:1, 1-46.
92. Musani AI. Treatment options for malignant pleural effusion. Curr Opin Pulm Med. 2009;15(4):380-7.
93. Muscat JE, Barish M. Epidemiology of talc exposure and ovarian cancer: A critical assessment. Comments Toxicol. 1998;6(5):327-35.
94. Muscat JE, Wynder EL. Re: "Perineal powder exposure and the risk of ovarian cancer". AM J EPIDEMIOL. 1997;146(9):786.
95. Moon M, J Park, B Choi, S Park, D Kim, Y Chung, N Hisanaga, I Yu. Risk assessment of baby powder exposure through inhalation. Official Journal of Korean Society of Toxicology. 27(3):137-147.
96. Narod SA. Talc and ovarian cancer. Gynecol Oncol. 2016.
97. Natow AJ. Talc: need we beware? Cutis. 1986;37(5):328-9.
98. Neill AS, Nagle CM, Spurdle AB, Webb PM. Use of talcum powder and endometrial cancer risk. Cancer Causes Control. 2012;23(3):513-9.
99. Newhouse ML. Cosmetic talc and ovarian cancer. Lancet. 1979;2(8141):528.
100. Ness RB. Ovarian cancer, inflammation and endometriosis. CME J Gynecol Oncol. 2003;8(1):33-40.
101. Ness, R. Does talc exposure cause ovarian cancer?:IGCS-0015 Ovarian Cancer. International Journal of Gynecological Cancer: Official Journal of the International Gynecological Cancer Society, 2015;25 Suppl. 1:51
102. Özyurtkan MO, Balci AE, Çakmak M. Predictors of mortality within three months in the patients with malignant pleural effusion. Eur J Intern Med. 2010;21(1):30-4.

103. Okada. Beyond foreign-body induced carcinogesis: impact of reactive oxygen species derived from inflammatory cells in tumorigenic conversion and tumor progression. Internal Journal of Cancer. 2007; 121(11):2364-72.
104. Park, Schidlkraut, Alberg, Bandera, Barnholtz-Sloan, Bondy, Crankshaw, Funkhouser, Moorman, Peters, Terry, Wang, Ruterbusch, Schwartz, Cote. Benign gynecology conditions are associated with ovarian cancer risk in African-American women: a case control study. Cancer Causes Control. 2018; Vol. 29, Issue 11, PP 1081-1091.
105. Pauler DK, Menon U, McIntosh M, Symecko HL, Skates SJ, Jacobs IJ. Factors influencing serum ca125ii levels in healthy postmenopausal women. Cancer Epidemiol Biomarkers Prev. 2001;10(5):489-93.
106. Pelfrene A, Shubik P. Is talc a carcinogen? A review of present data. NOUV PRESSE MED. 1975;4(11):801-3.
107. Porzio G, Marchetti P, Paris I, Narducci F, Ricevuto E, Ficorella C. Hypersensitivity reaction to carboplatin: Successful resolution by replacement with cisplatin. Eur J Gynaecol Oncol. 2002;23(4):335-6.
108. Radic, Vucak, Milosevic, Marusic, Vukicevic, Marusic. Immunosuppression induced by talc granulomatosis in the rat. Clinical and Experimental Immunology. 1988; 73(2):316-21.
109. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. 2017;14(1):9-32.
110. Reid, De Klerk, Musk. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. Cancer Epidemiology, Biomarkers & Prevention: a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology. 2011; 20(7):1287-98.
111. Rothman, K., Greenland, S., & Lash, TL. (2008). Modern Epidemiology, 3rd Edition. Philadelphia, PA: Lippincott Williams & Wilkins.
112. Reuter, Gupta, Chaturvedi, Aggarwal. Oxidative stress, inflammation, and cancer: how are they linked?. Free Radical Biology & Medicine. 2010; 49(11):1603-16.
113. Roe FJ. Controversy: cosmetic talc and ovarian cancer. Lancet. 1979;2(8145):744.
114. Ross. Geology, asbestos and health. Environmental Health Perspectives. 1974; 9:123-124.
115. Sagae S, Mori M, Moore MA. Risk factors for ovarian cancers: Do subtypes require separate treatment in epidemiological studies? Asian Pac J Cancer Preven. 2012;3(1):5-16.
116. Saka H, Shimokata K. State of the art: treatment of malignant pleural and pericardial effusions. Gan To Kagaku Ryoho. 1997;24 Suppl 3:418-25.
117. Salehi F, Dunfield L, Phillips KP, Krewski D, Vanderhyden BC. Risk factors for ovarian cancer: An overview with emphasis on hormonal factors. J Toxicol Environ Health Part B Crit Rev. 2008;11(3-4):301-21.Salvador S, Scott S, Francis JA, Agrawal A, Giede C. No. 344-Opportunistic Salpingectomy and Other Methods of Risk Reduction for Ovarian/Fallopian Tube/Peritoneal Cancer in the General Population. J Obstet Gynaecol Can. 2017;39(6):480-93.

118. Salvador S, Scott S, Francis JA, Agrawal A, Giede C. No 344-Salpingectomie opportuniste et autres méthodes pour réduire le risque de cancer de l'ovaire, de la trompe de Fallope et du péritoine dans la population générale. J Obstet Gynaecol Can. 2017;39(6):494-508.
119. Sanchez-Armengol A, Rodriguez-Panadero F. Survival and talc pleurodesis in metastatic pleural carcinoma, revisited: Report of 125 cases. CHEST. 1993;104(5):1482-5.
120. Shan, Lui. Inflammation: a hidden path to breaking the spell of ovarian cancer. Cell Cycle (Georgetorn, Tex). 2009; 8(19):31707-11.
121. Shedbalkar AR, Head JM, Head LR, Murphy DJ, Mason JH. Evaluation of talc pleural symphysis in management of malignant pleural effusion. J Thorac Cardiovasc Surg. 1971;61(3):492-7.
122. Shen N, Weiderpass E, Antilla A, Goldberg MS, Vasama-Neuvonen KM, Boffetta P, et al. Epidemiology of occupational and environmental risk factors related to ovarian cancer. Scandinavian journal of work, environment & health. 1998;24(3):175-82.
123. Shlebak AA, Clark PI, Green JA. Hypersensitivity and cross-reactivity to cisplatin and analogues. Cancer Chemother Pharmacol. 1995;35(4):349-51. Silva EG. The Origin of Epithelial Neoplasms of the Ovary: An Alternative View. Adv Anat Pathol. 2016;23(1):50-7.
124. Shoham Z. Epidemiology, etiology, and fertility drugs in ovarian epithelial carcinoma: Where are we today? FERTIL STERIL. 1994;62(3):433-48.
125. Sioris T, Sihvo E, Salo J, Räsänen J, Knuuttila A. Long-term indwelling pleural catheter (PleurX) for malignant pleural effusion unsuitable for talc pleurodesis. Eur J Surg Oncol. 2009;35(5):546-51.
126. Sueblinvong T, Carney ME. Ovarian cancer: risks. Hawaii Med J. 2009;68(2):40-6.
127. Sueblinvong T, Carney ME. Current understanding of risk factors for ovarian cancer. Curr Treat Options Oncol. 2009;10(1-2):67-81.
128. Tamaya T. Epidemiology of ovarian cancer. Nippon Rinsho. 2004;62 Suppl 10:435-40.
129. Tortolero-Luna G, Mitchell MF. The epidemiology of ovarian cancer. Journal of cellular biochemistry Supplement. 1995;23:200-7.
130. Tortolero-Luna G, Mitchell MF, Rhodes-Morris HE. Epidemiology and screening of ovarian cancer. OBSTET GYNECOL CLIN NORTH AM. 1994;21(1):1-23.
131. Trabert B, R Ness, W Lo-Ciganic, M Murph, E Goode, E Poole, L Brinton, et al (2014). Aspirin, Nonaspirin Nonsteroidal Anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium, Journal of the National Cancer Institute 106(2):djt431.
132. Urban N, Hawley S, Janes H, Karlan BY, Berg CD, Drescher CW, et al. Identifying post-menopausal women at elevated risk for epithelial ovarian cancer. Gynecol Oncol. 2015;139(2):253-60.
133. U.S. Department of Health & Human Service – Public Health Service, Agency for Toxic Substances and Disease Registry – "Toxicological profile for asbestos". https://www.atsdr.cdc.gov/toxprofiles/tp61.pdf.

134. Van Gosen B, H Lowers, S Sutley, and C. Gent. Using the geologic setting of talc deposits as an indicator of amphibole asbestos content. Environmental Geology. 45 (7):920-939.
135. Venter PF. Ovarian epithelial cancer and chemical carcinogenesis. Gynecol Oncol. 1981;12(3):281-5.
136. Verma A, Taha A, Venkateswaran S, Tee A. Effectiveness of medical thoracoscopy and thoracoscopic talc poudrage in patients with exudative pleural effusion. Singapore Med J. 2015;56(5):268-73.
137. Virta. The phrase relationship of talc and amphiboles in a fibrous talc sample. Vol. 8923 of the U.S. Dept. of the Interior, Bureau of Mines – Science.
138. Vitonis AF, Titus-Ernstoff L, Cramer DW. Assessing ovarian cancer risk when considering elective oophorectomy at the time of hysterectomy. Obstet Gynecol. 2011;117(5):1042-50.
139. Webb P, Gertig D, Hunter D. Ovarian Cancer. Textbook of Cancer Epidemiology: Oxford University Press; 2009.
140. Webb PM. Environmental (nongenetic) factors in gynecological cancers: Update and future perspectives. Future Oncol. 2015;11(2):295-307.
141. Whitworth JM, Schneider KE, Fauci JM, Bryant AS, Cerfolio RJ, Straughn JM. Outcomes of patients with gynecologic malignancies undergoing video-assisted thoracoscopic surgery (VATS) and pleurodesis for malignant pleural effusion. Gynecol Oncol. 2012;125(3):646-8.
142. Wehner AP. Biological effects of cosmetic talc. Food Chem Toxicol. 1994;32(12):1173-84.
143. Wehner AP. Is cosmetic talc 'safe'? Comments Toxicol. 1998;6(5):337-66.
144. Wehner AP. Cosmetic talc should not be listed as a carcinogen: Comments on NTP's deliberations to list talc as a carcinogen. REGUL TOXICOL PHARMACOL. 2002;36(1):40-50.
145. Wentzensen N, Wacholder S. Talc use and ovarian cancer: Epidemiology between a rock and a hard place. J Natl Cancer Inst. 2014;106(9).
146. Werner. Presence of asbestos in talc samples. Atemschutzinformation. 1982; 21:5-7.
147. Whysner J, Mohan M. Perineal application of talc and cornstarch powders: Evaluation of ovarian cancer risk. AM J OBSTET GYNECOL. 2000;182(3):720-4.
148. Wu, Song, Wei Zhu, Patricia Thompson, and Yusuf A. Hannun. 2018. "Evaluating Intrinsic and Non-Intrinsic Cancer Risk Factors." *Nature Communications* 9 (1): 3490. https://doi.org/10.1038/s41467-018-05467-z.

<u>Other Materials</u>

1. WCD000254-WCD000255
2. IMERYS210136-IMERYS210137
3. IMERYS241994-IMERYS242004
4. IMERYS242050
5. IMERYS322241-IMERYS322242

6. IMERYS422289- IMERYS422290
7. JNJ000087166-JNJ000087230
8. JNJ000251888-JNJ000251890
9. JNJ000261010-JNJ000261027
10. JNJ000460665-JNJ000460673
11. JNJ000526231-JNJ000526676
12. JNJAZ55_000000577-JNJAZ55_000000596
13. JNJAZ55_000003357
14. JNJAZ55_000012423-JNJAZ55_000012430
15. JNJI4T5_000004099-JNJI4T5_000004100
16. JNJI4T5_000006431-JNJI4T5_000006432
17. JNJMX68_000004996-JNJMX68_000005044
18. JNJNL61_000001534-JNJNL61_000001535
19. JNJNL61_000014431-JNJNL61_000014437
20. JNJNL61_000020359
21. JNJNL61_000052427
22. JNJNL61_000061857
23. JNJNL61_000063473
24. John Hopkins, Trial Testimony, *Berg v. Johnson & Johnson* 2013
25. Deposition Transcript & Exhibits – John Hopkins, Aug. 16 & 17, 2018, Oct. 26, 2018, Nov. 5, 2018
26. Deposition Transcript & Exhibits – Joshua Muscat, Sept. 25, 2018
27. Deposition Transcript & Exhibits – Julie Pier, Sept. 12 & 13, 2018
28. Deposition Transcripts - Linda Loretz, Oct. 2, 2018
29. Deposition Exhibits for Linda Loretz - Exh. 106, 107, 108, Oct. 2, 2018
30. Deposition Transcript of Alice Blount, Apr. 13, 2018
31. Educational report of Thomas Dydek
32. Expert report of Jack Siemiatycki.
33. Expert report of Laura Plunket (Oules).
34. Fair warning TalcDoc 15.
35. Fair warning TalcDoc 5- Exhibit 113 (JNJNL91_000022019).
36. Letter from Cancer Prevention Coalition to FDA re: Citizen's Petition seeking carcinogenic labeling on all cosmetic talc products, Nov. 17, 1994.
37. Letter from Cancer Prevention Coalition to FDA re: Citizen's Petition seeking a cancer warning on cosmetic talc products, May 13, 2008.
38. Letter from Personal Care Products Council to FDA re: Comments on Citizen's Petition to the Commissioner of the Food and Drug Administration Seeking a Cancer Warning on Talc Products, July 21, 2009.
39. Transcripts of CIR meeting (Unpublished)

40. Rothman, Pastides, Samet. Interpretation of epidemiologic studies of talc and ovarian cancer. 2000.

41. Zuckerman D, D Shapiro. Talcum Powder and Ovarian Cancer, National Center for Health Research, May 7, 2018 http://www.center4research.org/talcum-powder-ovarian-cancer/

EXHIBIT A

Sonal Singh, MD MPH
55 Lake Ave North
Worcester, MA 01655-0002 USA
Tel: 774 442 6611.
Sonal.Singh@umassmemorial.org

Education

MPH, Bloomberg School of Public Health, Johns Hopkins University
Baltimore, MD — 6/2005 to 5/2008

Internal Medicine Residency, Unity Health System, affiliate University of Rochester
Sch of Medicine and Dentistry, Rochester, NY — 7/2002 to 6/2005

MD, Patna Medical College, Patna, India — 12/91 to 05/1999

Academic Appointments

Associate Professor, Department of Family Medicine & Comm Health — 10/2016 to date
Department of Medicine, University of Massachusetts Medical School

Assistant Professor, Dept of Medicine, Johns Hopkins Univ SOM — 7/2009 to 9/2016

Assistant Professor, Center for Public Health and Human Rights
Bloomberg School of Public Health, JHU (joint) — 7/2009 to 9/2016

Assistant Professor, Department of Medicine, Wake Forest University — 7/2007 to 6/2009

Instructor, Department of Medicine, Wake Forest University — 7/2005 to 06/2007

Employment History

Associate Professor, Department of Fam Medicine & Comm Hlth — 10/2016-present
Meyers Primary Care Institute & Department of Medicine (Joint)
University of Massachusetts Medical School
Role: Clinician- Investigator

Associate Professor, Department of Quantitative Health Sciences — 10/2018-present
University of Massachusetts Medical School
Role: Clinician- Investigator

Assistant Professor, Dept of Medicine, Johns Hopkins University. — 7/2009 to 9/2016
Role: Clinician- Investigator

Assistant Professor, Department of Medicine, Wake Forest University — 7/2007 to 6/2009
Role: Clinician- Educator

Instructor, Department of Medicine, Wake Forest University — 7/2005 to 6/2007

Role: Clinician- Educator

Residency (Medicine) Unity Healthy System, affiliate of the University of Rochester, Rochester, NY 7/2002 to 6/2005

Role: PGY 1, PGYII and PGY III Internal Medicine Resident

Research Associate, Clinical Pharmacology, Ohio State University 3/2001 to 6/2002
Role: Research assistant in clinical trials

Voluntary Research Associate, Clinical Pharmacology, Ohio State University 8/2000 to 2/2001
Role: Research assistant in clinical trials

USMLE STEP 1, II, III and Clinical Skills Exam Preparation 2/2000 to 7/2000
Role; Medical student

Resident, Medicine, Patna Medical College, Patna, Bihar, India 2/1998 to 1/2000
Role: Junior Resident in Medicine

Compulsory rotatory internship, Patna Medical College, Patna, India 12/97 to 12/98
Role: Fulfilling requirements for completion of medical degree in India

Certification and Licensure

Diplomate, American Board of Internal Medicine 8/2005-12/25

Massachusetts Board of Physicians 8/2016-8/2019

Physicians and Surgeons of Maryland (Inactive) 2009-2017

North Carolina Medical Board (Inactive) 2005 to 2009

Professional Memberships and Activities

Massachusetts Medical Society 2017-current

American College of Physicians 2003-2019

International Society of Pharmacoepidemiology 2011-current

Society of General Internal Medicine 2003 to 2016

International Society of Pharmacoeconomic Outcomes Research 2016 to 2017

Academy Health 2013

Global Health Council 2006 to 2010

Honors and Awards

Finalist W. Leigh Thompson Excellence in Research: Faculty Award, JHU 2016

Visiting Professor, Department of Medicine, Univ of Alabama 2013

3rd Best Abstract (trainee) 29th ICPE Montreal, Canada 2013

Bruce Squires Award for the Best Research Paper, CMAJ 2011

Scholars Abstract Award, Society for Clinical and Translational Sciences. 2010

Society of General Internal Medicine Clinical Investigator Award (Mid-Atlantic) 2010

Elected, Delta Omega Honorary Public Health Society, Johns Hopkins University 2008

Master Teacher Award, WFUSOM 2008

Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM 2007

Tinsley R Harrison Faculty Outpatient Teaching Award, WFUSOM 2006

Senior–Resident Scholarship award, Unity Health System, NY 2005

ACP Health and Public Policy Scholarship, NY 2005

Committee Assignments and Administrative Services

American College of Physicians, Massachusetts Chapter, Health Policy Committee 2018

Chairs Advisory Council, Department of Fam Medicine & Comm Hlth 10/2016-present

American College of Chest Physicians, Cough Guideline Expert Panel 2017- present

Associate faculty, Welch Ctr for Prevention, Epi & Clin Research, JHU 2015 to 2016

Associate-Director, Center for Drug Safety and Effectiveness, JHU 2013 to 2016

Affiliate faculty, Center for Hlth Services and Outcomes Research, Johns Hopkins Bloomberg School of Public Health 2012 to 2016

World Health Organization, International Agency of Research on Cancer (IARC) Monograph- 108 Working group, Lyon, France. 2013

Preferred Items for Reporting of Systematic Reviews and Meta-analysis of harms Working Group Alberta Canada. 2012

Member, Health & Human Rights Working Group, JHU Center for Aids Research 2012

Core faculty, Center for Public Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2009 to 2016

Core faculty, Evidence-Based Practice Center, JHU 2009 to 2016

Medical Director, Outpatient Clinic, WFUSOM 7/2005-6/2009

Teaching Activities

Classroom

Comparative effectiveness research (2 cr), Johns Hopkins Medicine 2015 to 2016
Role: Developed course in CER for MD and MD/PhD trainees in the CTSA

Health and Human Rights, Johns Hopkins Bloomberg School of Public Health 2011 to 2015
Role: Annual lecture in the course for MPH students

Health Economic, Johns Hopkins Bloomberg School of Public Health 2013
Role: Annual lecture in the course for master's students

Pharmacoepidemiology, Johns Hopkins Bloomberg School of Public Health 2011-2015
Role: Annual lecture in the course for Masters and Doctoral students

Evidence-based Medicine, Johns Hopkins University School of Medicine 2012
Role: Course facilitator

Intro to Clinical Investigation, Johns Hopkins University School of Medicine 2012
Role: Annual lecture in the course

Clinical Epidemiology, Johns Hopkins Bloomberg School of Public Health, 2010-2014
Role: Annual lecture in the course

Patient Physician and Society, Johns Hopkins University School of Medicine 2009
Role: Course facilitator

Clinical Teaching

Outpatient medicine 2016-2018

Role: Precepting residents and medical students in clinic at University of Massachusetts Medical School

Evidence Based Medicine 2012-2014
Role: Developed a novel course to teach Evidence based Medicine to Osler medical residents at Johns Hopkins University School of Medicine

Outpatient medicine 2005 to 2009
Role: Precepting residents in clinic at Wake Forest University

Inpatient Medicine 2005 to 2009
Role: Precepting internal medicine residents at Wake Forest University

Trainee /Junior Faculty Name	Mentoring Role	Title of Research Project/Paper	Current Position and Institution	Training Period
Univ of Massachusetts				
Mayuko Itofukunaga, MD	Faculty mentor	Systematic review of decision aids for lung cancer screening	Assistant Professor- Pulmonary Medicine and Critical Care	2017-18
Nathaniel, Erskine MD, PhD (student)	Scholarly activity	SR of herpes zoster and cardiovascular disease	MD/PhD Student Umass Med School	2017
Richeek Pradhan MS	Scholarly activity	Comparison of data on Adverse events	Phd Student McGill University	2017-18
Johns Hopkins Univ				
Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student	2018
Geetha Iyer, MD	Faculty mentor	Multiple Pharmacoepidemiologic studies	Doctoral student, HSPH	2015-16
Sathiya Priya Marimathu	Faculty mentor	Generic drugs and patient oriented outcomes	MHS Student, JHMI	2015-16
Yohalakshmi Chelladurai, MD, MPH	RA Scholarly activity	Review of varenicline	Resident physician, Mercer, Atlanta	2013
Hsien-Yen Chang PhD	Faculty mentor	Pharmacoepidemiologic studies	Assistant Scientist at JHU	2011-15
Hasan Shihab, MD, MPH	RA Scholarly activity	Review of GLP-based therapies	Resident, Franklin Square, Baltimore	2013-14
Joshua Sclar, MD, MPH	Scholarly activity	Systematic review of attacks on health workers	General Preventive Medicine Resident	2013
Crystal Ng, MPH	Scholarly activity	Human Rights measures	MPH Student, JHSPH	2013
Ekta Agarwal, MPH	Capstone	Safety of novel anticoagulants	MPH student JHSPH	2013
Meijia Zhou, MHS	Scholarly activity	Adherence to novel anticoagulants	Doctoral student, Univ of Pennsylvania	2013
Kaitlin Hayman, MD	Capstone	SR of the impact of disasters On CVD outcomes	MPH student, JHSPH	2013
Wenze Tang, MPH	Scholarly activity	SCCS analysis of GIB bleeding with dabigatran	Doctoral student, HSPH	2013

Omar Mansour	Scholarly activity	SGLT2inhibitors and cardiovascular outcomes	Masters student JHSPH	2018
Shabana Walia MD	Scholarly activity	SR of CVD among refugees and displaced	ER physician, UT Houston	2016-2018
Wake Forest Univ				
Aman Amin, MD	Resident	Inhaled corticosteroids and pneumonia	Practicing internist, NC	2007-09
Apurva Trivedi, MD	Scholarly activity	SSRIs and bleeding	Gastroenterologist	2007-09
Other institutions				
Tonya Breaux-Shropshire PhD, MPH	Scholarly activity	Systematic review	Post-doctoral trainee, UAB	2015
Abhay Kumar, MD	Resident Scholarly activity	Wernicke encephalopathy after gastric bypass: systematic review	Assistant Professor St Louis University	2007

Current Grants and Contracts
Grants
(Ming Tai-Seale) 2/2016-12/2021
PCORI
Improving Patient-Centered Communication in Primary Care: A Cluster Randomized Controlled Trial of the Comparative Effectiveness of Three Interventions
The aim is to compare three interventions to improve patient communication in primary care
Role: co-investigator

(PI Jerry Gurwitz) 08/2018- 09/2019
NIH/NIA-1 R56 AG061813-01
Project Title: Controlling and Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)
Role : co-investigator
The aim is to develop interventions to prevent prescribing cascades among those with Alzheimer's related Dementia (ADRD)

Past Grants
Death Data Exploration 08/01/17- 03/02/18
FDA Foundational Elements 3 HHSF223200910006I
Task Order Number: HHSF22301012T
Efforts to Develop the Sentinel Initiative HHSF223200910006I.
Role (Project Lead)

Effect of Therapeutic Class on Generic Drug Substitutions. 2014-2016
U01FD005267-01 (PI, Jodi Segal)

FDA 349,480
Role: Co-Investigator 0.6 CM

Comparative effectiveness Research & The Cochrane Eyes and Vision Group 2013-2016
U01 EY020522 (PI, Kay Dickersin)
NIH/NEI 825,397
Role: Co-Investigator 2.4 CM

Systematic review of gabapentin for neuropathic pain using multiple data sources 2015-2016
(PI, Caleb Alexander)
FDA Center of Excellence in Regulatory Science
Role: Co-Investigator (20% effort)

Integrating multiple data sources for meta-analysis to improve patient-centered outcomes research 2014-2016
(PI- Dickersin)
PCORI (ME-1303-5785) $698,174
Role: Advisor (2% effort)

Development of a scale for human rights violations. 2013-2014
(PI, Chaisson & Beyrer)
NIH Johns Hopkins Center for AIDS Research $ 18,873
Role: Pilot Awardee

Comparative effectiveness review of therapeutic options for obesity in the Medicare population.
Johns Hopkins Evidence Based Practice Center. 2013-2014
PI (Eric Bass)
AHRQ $125,000
Role: Project Principal Investigator (20% effort)

Center for Excellence in Comparative Effectiveness Education 2012-2013
PHRMA Foundation (PI Jodi Segal) Total Direct Cost: $250,000
Role: Co-investigator (5% effort)

A multi criteria decision analysis to assist with regulatory decisions around benefit and risk
Partnership in Applied Comparative Effectiveness Science: 2010 to 2013
PI (PI, Jodi Segal).
FDA $3,509,657
Role: Project Principal Investigator (25% effort)

Combination therapy vs. intensification of statin mono-therapy: An update. 2012-2013
PI (E. Bass- P.I of EPC.)
AHRQ
Role: Advisor (5% effort)

Troponin cardiac marker during renal impairment. 2012-2013
(E. Bass- P.I of EPC.)
Agency for Health Care Quality and Research
Role: Advisor (5% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
US Institute of Peace
Role: Co-investigator (10% effort)

To develop an instrument for attacks on health workers. 2012-2013
PI (Len Rubenstein)
McArthur Foundation $434,782
Role: Co-investigator (15% effort)

To conduct a benefit and harm assessment of *roflumilast* in COPD. 2012-2013
Johns Hopkins ICTR
Role: Co-investigator (5% effort)

To develop a China-JHU consultation for civil society public health professionals. 2012
Open Society Foundation $49,534
Role: PI (20% effort). Proposal for a public health training program.

PACER. 2012
PI (Rothman)
Google-Flu
Role: Coinvestigator (5%) Systematic reviewer and meta-analysis expert.

Methods for Balancing Benefits and Harms in Systematic Reviews
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $188,871
Role: Project Task Leader and co-Investigator (10% effort)

Comparative effectiveness review of Meditation Programs for Stress and Wellbeing
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Task Leader and co-Investigator (15% effort)

Comparative effectiveness review of prevention of VTE in special populations
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2011-2012
AHRQ $375,666
Role: Project Principal Investigator (20% effort)

To prevent and respond to gender-based violence (GBV) in refugee and conflict-affected populations. 2010-2011
(PI, Vu & Rubenstein) $293,946
Role: Co-investigator (10% effort)

Comparative effectiveness review of oral hypoglycemic medications
Johns Hopkins Evidence Based Practice Center. (PI, Bass) 2009-2010
AHRQ $125,000
Role: Co- Investigator (0% effort)

Johns Hopkins Clinical Research Junior Faculty Award. 2009-2012
NIH-KL2
ICTR
Role: Recipient (75% salary support)

Measuring exposure to human rights violations among men who have sex with men.
(PI, Mullany). 2009-2010
Center for Global Health Johns Hopkins $50,000
Role: Co-investigator (0% effort).

Research ethics for conducting research in vulnerable populations and unstable settings.
(PI, Mills) 2007-2009
CIHR $99, 887
Role: Co-investigator (10% effort).

Patents None.

<u>Editorial work</u>

Editor-in-chief and founder

BMC Conflict and Health 2007-12

Editorial Board Membership

Evidence Based Medicine (BMJ Group of Journals) 2017-current
Drug Safety 2008-16
American College of Physicians-PIER

Grant review 2012-current

Medical research foundation of New Zealand
Johns Hopkins Center for Public Health and Human Rights
Junior Faculty Research Grants
Medical Research Council of South Africa
Catalina Health Technology Assessment, Spain
Diabetes, UK
Johns Hopkins Medicine Research Council Synergy Awards
Johns Hopkins Institute for Clinical and Translational Research

Peer Review

1. *Acta Diabetologica*
2. *American Heart Journal*
3. *American Journal of Addictions*
4. *American Journal of Cardiovascular Drugs*
5. *American Journal of Managed Care*
6. *American Journal of Psychiatry*
7. *Annals of Internal Medicine*
8. *Annals of Medicine*
9. *Australian Medical Journal*
10. *BMJ*
11. *BMC Clinical Pharmacology*
12. *British Journal of Clinical Pharmacology*
13. *Bulletin of the World Health Organization*
14. *Chest*
15. *Circulation*
16. *Canadian Medical Association Journal*
17. *Clinical Pharmacology and Therapeutics*
18. *Clinical Trials*
19. *Cardiovascular Drugs & Therapy*
20. *Cochrane Collaboration*
21. *Disasters*
22. *Diabetolgia*
23. *Drug and Alcohol Dependence*
24. *Diabetes Obesity and Metabolism*
25. *Drug Safety*
26. *Epidemiology*
27. *European Journal of Neurology*
28. *European Journal of Pharmacology*
29. *European Respiratory Journal*
30. *Expert Opinion in Drug Safety*
31. *Global Public Health*
32. *Health Policy*
33. *International Journal of Epi*
34. *International Journal of Obesity*

35. Journal of the American College of Cardiology
36. Journal of the American Medical Association (5 in last 12 mo)
37. Journal of the American Medical Association-Internal Medicine
38. Journal of Cardiac Failure
39. Journal of Medical Case Reports
40. Journal of the Pancreas
41. Journal of General Internal Medicine
42. Medscape General Medicine
43. Medical Journal of Australia
44. Nephrology Dialysis Transplantation
45. North Carolina Medical Journal
46. Nutrition, Metabolism & Cardiovascular Diseases
47. Pediatric Infectious Disease Journal
48. Pharmacoepidemiology & Drug Safety-Best Reviewer Award 2013
49. Public Library of Science Medicine
50. Primary Care Respiratory Journal
51. Pediatrics
52. Research Synthesis Methods
53. Respiratory Medicine
54. Respirology
55. Southern Medical Journal
56. The Lancet
57. Thorax
58. Tropical Medicine & International Health

Abstracts and Presentations

Oral Presentations

National/International

1. GLP-1-based therapies and risk of pancreatitis: A matched case-control study. 29th International Society of Pharmacoepidemiology, Annual Meeting, Montreal Convention Center, August 26. Montreal, Quebec, Canada.2013
2. GLP-1 based therapies and risk of pancreatitis. 36th SGIM Annual Meeting, Denver, Colorado Posters. 2013
3. Risk of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of randomized controlled trials and observational studies, Society of General Internal Medicine, Minneapolis, Minnesota. 2011

4. Odds of fractures with inhaled corticosteroids in COPD: Systematic review and meta-analysis of clinical trials and observational studies, 27th International Society of Pharmacy-Epidemiology, Annual Meeting, Hyatt Regency August 24th. Chicago, Illinois. 2011

Local/Regional
Not applicable

Posters
National/International Meetings

1. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. International Society of Pharmacoepidemiology, Prague, August 24, 2018.
2. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. Health Care Systems Research Network, San Deigo, March 22, 2017.
3. GLP-1 based therapies and risk of pancreatitis. Pancreatitis, Diabetes, and Pancreatic Cancer Workshop. NIH, Bethesda, Maryland. 2013
4. Thiazolidinediones and risk of bladder cancer: A systematic review and meta-analysis. 36th SGIM Annual Meeting, Denver, Colorado.2013
5. Who is the patient's doctor? Primary care responsibility and co-management relationships among generalist and non-generalist physicians in the National Ambulatory Care Survey, 2002 SGIM 29th Annual Meeting, Los Angeles, California.2006
6. The educational value of case reports from the SGIM national meeting in the internal medicine clerkship. SGIM 29th Annual Meeting, Los Angeles, California.2006
7. Using IPod technology to create a self-guided clinic tour for resident orientation SGIM 29th Annual Meeting, Los Angeles, California.2006
8. Narcotic management in chronic non-malignant pain. A survey of resident's knowledge and attitudes. SGIM 29th Annual Meeting, Los Angeles, California.2006
9. Formulary conversion programs pose a significant risk to patients, SGIM 27th Annual Meeting, Chicago, Illinois.2004

Local regional meetings
Inhaled corticosteroids and the risk of fractures in COPD: A systematic review and meta-analysis. DOM Annual retreat, Johns Hopkins University 2011

Invited presentations
National/International

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. NIH Collaboratory Grand Rounds [Web] March 2, 2018
2. Resurgence of hepatocellular carcinoma in the era of oral direct acting antivirals. Cause or Consequence? Fundamentals of Biomedicine Seminar Series. Texas Tech University Health Sciences Center. El Paso, Texas Dec 13, 2017

3. Aligning evidence with preferences: Methodological Challenges and Opportunities. - Department of Medicine. Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
    - Dartmouth-Hitchcock Medical Center, Dartmouth, New Hampshire, June 15, 2016
    - Department of Health Services and Research, Michael De-Bakey VA and Baylor University, Houston, Texas, May 16, 2016.
    - Meyers Primary Care Institute and Department of Family and Community Medicine, University of Massachusetts, Massachusetts, March 31 and June 9 2016.
    - VA Center for Chronic Disease and Outcomes Research, Minnesota VA, March 2016.
    - Department of Medicine. University of Central Florida, Orlando, Florida, November 2015.
    - Center for Health Policy and Research Grand Rounds. UC Davis, Sacramento California, Oct 9 2015;
    - Center for Evidence and Outcomes, Agency for Health Care Research and Quality. Gaithersville Maryland, August 31, 2015.
4. Risks of Spiriva Respimat outweigh its benefit: A Debate. Inhalation Asia, University of Hong Kong, Department of Pharmacology and Pharmacy, Hong Kong. 2013
5. GLP-1-based therapies and risk of pancreatitis. Center for Clinical Epidemiology and Biostatistics Seminar Series, Philadelphia, Pennsylvania. 2013
6. Visiting Professor. Department of Medicine. University of Alabama. 2013
7. Value based health care: Can shared decision making methods get us there? Center for Value and Effectiveness, Medicine Institute, Cleveland Clinic, Noon Conference.2013
8. Role of Multi-criteria decision analysis in regulatory policy
    - Stanford Prevention Research Center, Stanford University, Palo Alto, Stanford, California. 2013
    - South Carolina College of Pharmacy, Columbia, South Carolina.2013
    - Department of Medicine. UC Davis, Sacramento, California.2013
    - Department of Clinical Sciences, UT Southwestern, Dallas, Texas.2013
    - Department of Medicine, Geisenger Medical Center, Danville, Pennsylvania. 2013
9. Weighing benefits and risks: Role of shared decision making in type 2 diabetes. CTSA Grand Rounds, Mayo Clinic, Rochester, Minnesota. 2013
10. Are long-acting muscarinic agents safe for patients with COPD: A Debate. Airway Vista, Asan Medical Center, Seoul, Korea
11. Academia and industry collaboration for cardiovascular risk mitigation. CBI and Applied Clinical Trials. 6th Annual Summit, Closing Address. Ritz Carlton, Arlington, Virginia.2012
12. Varenicline: Where are we today? Tobacco Disease Research Program, UCSF. San Francisco California. Varenicline debate.2012
13. The Maoist Insurgency in Nepal: Health Systems Challenges and Opportunities Conference on Health in Fragile States: Challenges for the Next Decade. United States Institute of Peace. Washington DC.2011

14. Standards of Care and the Role of Community Advocacy in Clinical Trials. Clinical Research in Developing Countries, IIIrd Annual Marcus Evans Conference, Washington, DC.2008
15. Nepal-A Case study. Integrating public health methods into Conflict Analysis. Norman Patterson School of International Affairs, Carleton University, Ottawa, Canada.2007

Local/Regional

1. Oral direct acting antivirals and the incidence or recurrence of hepatocellular carcinoma. Research Seminar Series, Department of Family Medicine and Community Health. University of Massachusetts Medical School. June 15.2018
2. Safety of novel anticoagulants vs warfarin- a case study using complementary study designs. Quantitative Health Sciences, University of Massachusetts Medical School, February 28, 2017
3. GLP-1-based therapies and risk of pancreatic adverse events. University of Maryland, Division of Endocrinology, Metabolism and Nutrition, Grand Rounds, Baltimore, Maryland. 2013
4. Thiazolidinediones and Patient-Oriented Outcomes in Type 2 Diabetes, GIM Grand Rounds. Johns Hopkins University School of Medicine. 2012
5. Patient-Centered Benefit and Risk Assessment. Center for Health Services and Outcomes Research. Johns Hopkins University 2012
6. Varenicline and cardiovascular and neuropsychiatric adverse events: Do benefits outweigh risks? Welch Center Grand Rounds. Johns Hopkins University. 2011
7. The new wave, HIV, Human Rights and Men who have Sex with Men in Nepal. Johns Hopkins Bloomberg School of Public Health, 2011.
8. Network Meta-analysis and Serious Adverse Events. Network Meta-Analysis Methods Workshop. Johns Hopkins Bloomberg School of Public Health. 2010
9. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2008
10. How Safe Are Our Drugs and How Do We Know? North Carolina ACP, Durham.2008
11. Clinico Pathologic Conference. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
12. Globalization and Health Equity: An emerging Challenge for Academic Medicine. Internal Medicine Grand Rounds. Wake Forest University School of Medicine, 2007
13. Thiazolidinediones and Cardiovascular Disease: The Seduction of Common Sense. Epidemiology Seminar Series, Public Health Sciences. Wake Forest University 2007

Workshops and Precourses

1. ISPOR National Meeting, Next Generation Comparative Effectiveness Research- Are we getting organized to facilitate research for the individual patient? Washington, DC May 24, 2016 (workshop)
2. SGIM national meeting, developing high-quality search strategies for systematic reviews. 2010
3. SGIM national meeting, Systematic Review. 2009

Peer reviewed original research publications (reverse chronological order)

*Trainees **

1. **Singh S**, Fouyazi H, Anzuoni K, Goldman L, Min JY, Griffin M, Grijalva CG, Morrow JA, Whitmore C, Leonard CE, Selvan M, Nair V, Zhou Y, Toh S, Petrone A, Williams J, Fazio-

Eynullayeva E, Swain R, Cole DT, Andrade S. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review. Drug Safety 2018 (accepted)

2. **Singh S,** Zeiman S, Alan Go, Fortmann S, Wenger N, Fleg JL, Radziszewska B, Stone NJ, Zoungas S, Gurwitz J. Statins for Primary Prevention in Older Adults – Moving toward Evidence-Based Decision-Making. *J Am Geriatr Soc. 2018 Oct 2. doi: 10.1111/jgs.15449. [Epub ahead of print]*
3. Tisminetzky M, Nguyen HL, Gurwitz J, McManus D, Gore J, **Singh S**, Yarzebski J, Goldberg RJ. Magnitude and impact of multiple chronic conditions with advancing age in older adults hospitalized with acute myocardial infarction. *International Journal of Cardiology. Published* Online: August 22, 2018. https://doi.org/10.1016/j.ijcard.2018.08.062.
4. Chang HY, **Singh S**, Mansour O, Baksh S, Alexander GC. Association Between Sodium-Glucose Cotransporter-2 (SLGT-2) Inhibitors and Lower Extremity Amputation: A Retrospective Cohort Study. JAMA Internal Medicine 2018. 10.1001/jamainternmed.2018.3034 http://dx.doi.org/10.1001/jamainternmed.2018.3034. August 13, 2018
5. Birring SS, Kavanagh JE, Irwin RS, Keogh K, Lim KG, Ryu JH; **CHEST Expert Cough Panel**. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. Chest. 2018 Jul 20. pii: S0012-3692(18)31075-4. doi: 10.1016/j.chest.2018.06.038. [Epub ahead of print]
6. **Singh S**, Nautiyal A, Loke YK. Oral Direct-acting antivirals and the incidence or recurrence of hepatocellular carcinoma: a systematic review and meta-analysis. Frontline Gastroenterology Published Online First: 30 July 2018. doi: 10.1136/flgastro-2018-101017
7. Chang AB, Oppenheimer JJ, Rubin BK, Weinberger M, Irwin RS; **CHEST Expert Cough Panel**. Chronic Cough Related to Acute Viral Bronchiolitis in Children. Chest. 2018 Apr 26. pii: S0012-3692(18)30632-9. doi: 10.1016/j.chest.2018.04.019. [Epub ahead of print]
8. Haar RJ, Risko CB, **Singh S,** Rayes D, Albaik A, Alnajar M, et al. (2018) Determining the scope of attacks on health in four governorates of Syria in 2016: Results of a field surveillance program. PLoS Med 15(4): e1002559. https://doi. org/10.1371/journal.pmed.1002559
9. Pradhan R, * **Singh S.** Comparison of data on Serious Adverse Events and Mortality in ClinicalTrials.gov corresponding journal articles and medical reviews: A cross-sectional analysis. Drug Safety 2018 Apr 11. doi: 10.1007/s40264-018-0666-y. [Epub ahead of print]
10. Wu CH, Tu ST, Chang YF, Chan DC, Chien JT, Lin CH, **Singh S**, Dasari M, Chen JF, Tsai KS. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. Bone. 2018 2018 Jun; 111:92-100. doi: 10.1016/j.bone.2018.03.018. Epub 2018 Mar 16
11. Field SK, Escalante P, Fisher DA, Ireland B, Irwin RS; **CHEST Expert Cough Panel**. Cough Due to TB and Other Chronic Infections: CHEST Guideline and Expert Panel Report. Chest. 2018 Feb;153(2):467-497. doi: 10.1016/j.chest.2017.11.018. Epub 2017 Nov 28.
12. Erkskine NA, *Tran H, Levin LL, Ulbricht CM, Fingeroth JD, Kiefe CI, Goldberg RJ, **Singh S.** A systematic review and meta-analysis on herpes zoster and the risk of cardiac and cerebrovascular events. PLoS One 2017 Jul 27;12(7): e0181565
13. **Singh S**. Nautiyal A. Aortic dissection and aortic aneurysms associated with fluoroquinolones: a systematic review and meta-analysis of observational studies. American Journal of Medicine 2017;130(12):1449-1457

14. Marimuthu S, Iyer G, * Segal JB, **Singh S**. Patient-relevant outcomes associated with generic tamsulosin, levothyroxine, and amphetamine in the FAERS: A pilot study. J Comp Eff Res. 2017;6(5):437-447.
15. Iyer G, *Marimuthu S, *Segal JB, **Singh S**. An algorithm to identify generic drugs in the FDA Adverse Event Reporting System. Drug Safety 2017 2;40(9):799-808.
16. Tang W, *Chang HY, *Zhou M, * **Singh S**. Risk of gastrointestinal bleeding among dabigatran users-a self-controlled case series analysis. *Sci Rep* 2017 Jan 20; 7:40120. doi: 10.1038/srep40120.
17. Onasanya O, Iyer G, * Lucas E, Lin D, **Singh S**, Alexander GC. Association between exogenous testosterone and cardiovascular events: an overview of systematic reviews. *Lancet Diabetes Endocrinol*. 2016 ;4(11):943-956
18. **Singh S**, Wright EE, Kwan AY, Thompson JC, Syed IA, Korol EE, Waser NA, Yu MB, Juneja R. Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2017;19(2):228-238
19. Alexander GC, Iyer G, Lucas E, Lin D, **Singh S**. Cardiovascular risks of exogenous testosterone among men. *Am J Med*. 2017 ;130(3):293-305
20. Houston KT, Shrestha A, Kafle HM, **Singh S**, Mullany L, Thapa L, Surkan PJ 1. Social isolation and health in widowhood: A qualitative study of Nepali widows' experiences. *Health Care Women Int*. 2016 ;37(12):1277-1288
21. Zorzela, L., Loke, Y.K., Ioannidis, J.P., Golder, S., Santaguida, P., Altman, D.G., Moher, D., Vohra, S., Boon, H., Clark, J., Derry, S., Gallivan, J., Gardiner, P., Gøtzsche, P., Loder, E., Napoli, M., Pilkington, K., Shekelle, P., **Singh S**, Witt, C., Lasserson, T., Wu, T., Shamseer, L., Mulrow, C. PRISMA harms checklist: improving harms reporting in systematic reviews. *BMJ* 2016;352: i157.
22. Fain KM, Yu T, Li T, Boyd CM, **Singh S**, Puhan MA, Evidence Selection for a Prescription Drug's Benefit-Harm Assessment: Challenges and Recommendations, *JCE* 2016 Jun;74:151-7
23. Vu A, Wirtz A, Pham K, **Singh S**, Rubenstein L, Glass N, Perrin N. Psychometric properties and reliability of the Assessment Screen to Identify Survivors Toolkit for Gender Based Violence (ASIST-GBV): results from humanitarian settings in Ethiopia and Colombia. *Confl Health*. 2016 Feb 9; 10:1.
24. Wirtz, AL, Glass N, Pham K, Perrin N, Rubenstein LS, **Singh S**, Vu A. Comprehensive development and testing of the ASIST-GBV, a screening tool for responding to gender-based violence among women in humanitarian settings. *Conflict and Health* 201610:7 DOI: 10.1186/s13031-016-0071-z
25. Hayman KG, *Sharma D, Wardlow RD II, **Singh S**. Burden of cardiovascular morbidity and mortality following humanitarian emergencies: a systematic literature review. *Prehosp Disaster Med*. 2015;30(1):1-9.
26. Chang HY, *Zhou M, * Tang W, * Alexander GC, **Singh S**. Risk of gastrointestinal bleeding associated with oral anticoagulants: population based retrospective cohort study. *BMJ*. 2015;350:h1585 (editorial by Mary S Vaughn).

27. Abraham NS, **Singh S**, Alexander GC, Heien H, Haas LR, Crown W, Shah ND. Comparative risk of gastrointestinal bleeding with dabigatran, rivaroxaban, and warfarin: population-based cohort study. *BMJ*. 2015;350:h1857.
28. Chang HY, Hsieh CF, **Singh S**, Tang W, Chiang YT, Huang WF. Anti-diabetic therapies and the risk of acute pancreatitis: a nationwide retrospective cohort study from Taiwan. *Pharmacoepidemiol Drug Saf*. 2015 Jun;24(6):567-75
29. Maruthur NM, Joy SM, Dolan JG, Shihab HM, **Singh S**. Use of the Analytic Hierarchy Process for medication decision-making in type 2 diabetes. *PloS One*. 2015 ;10(5): e0126625.
30. Breaux-Shropshire TL, * Judd E, Vucovich L, Shropshire TS, **Singh S**. Does home blood pressure monitoring improve patient outcomes? A systematic review comparing home and ambulatory blood pressure monitoring on blood pressure control and patient outcomes. *Integrated Blood Pressure Control* 2015 3; 8:43-9.
31. Zhou M, *Chang HY, Segal JB, Alexander GC, **Singh S**. Adherence to a novel oral anticoagulant among patients with atrial fibrillation. *J Manag Care Spec Pharm*. 2015; 21(11):1054-62.
32. Puhan MA, Yu T, Stegeman I, Varadhan R, **Singh S**, Boyd CM. Benefit-Harm Analysis and Charts for Individualized and Preference-Sensitive Prevention - The example of low dose aspirin for primary prevention of cardiovascular disease and cancer. *BMC Med*. 2015; 13:250.
33. Mayo-Wilson E, Hutfless S, Li T, Gresham G, Fusco N, Ehmsen J, Heyward J, Vedula S, Lock D, Haythornthwaite J, Payne JL, Cowley T, Tolbert E, Rosman L, Twose C, Stuart EA, Hong H, Doshi P, Suarez-Cuervo C, **Singh S**, Dickersin K.Integrating multiple data sources (MUDS) for meta-analysis to improve patient-centered outcomes research: a protocol for a systematic review. *Syst Rev* 2015; 4(1).
34. Morton MJ, DeAugustinis ML, Velasquez CA, **Singh S**, Kelen GD. Developments in Surge Research Priorities: A Systematic Review of the Literature Following the Academic Emergency Medicine Consensus Conference, 2007-2015. *Acad Emerg Med*. 2015 ;22(11):1235-52.
35. *Shihab HM, Akande T, Armstrong K, **Singh S**, Loke YK. Risk of pancreatic adverse events associated with the use of glucagon-like peptide-1 receptor agonist and dipeptidyl peptidase-4 inhibitor drugs: A systematic review and meta-analysis of randomized trials. *World J Meta-Anal* 2015; 3(6): 254-283
36. Haut ER, Garcia LJ, Shihab HM, Brotman DJ, Stevens KA, Sharma R, Chelladurai Y, Akande TO, Shermock KM, Kebede S, Segal JB, **Singh S**. The Effectiveness of Prophylactic Inferior Vena Cava Filters in Trauma Patients: A Systematic Review and Meta-analysis. *JAMA Surg* 2014; 149(2):194-202
37. **Singh S**, Ambrosio M, Semini I, Tawil O, Saleem M, Imran M, Beyrer C. Revitalizing the HIV response in Pakistan: a systematic review and policy implications. *Int J Drug Policy* 2014;25(1):26-33.
38. Turner LW, Nartey D, Stafford RS, **Singh S**, Alexander GC. Ambulatory Treatment of Type 2 Diabetes Mellitus in the United States, 1997-2012. *Diabetes Care.* 2014;37(4):985-92
39. Yu T, Fain K, Boyd C, Varadhan R, Weiss CO, Li T, **Singh S**, Puhan MA. Benefits and harms of roflumilast in moderate to severe COPD. *Thorax* 2014; 69:616-22

40. Turner RM, Kwok CS, Chen-Turner C, Maduakor CA, **Singh S**, Loke YK. Thiazolidinediones and associated risk of Bladder Cancer: a Systematic Review and Meta-analysis. *Br J Clin Pharmacol.* 2014 78(2):258-7

41. Goyal M, **Singh S,** Sibinga E, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron D, Shihab HM, Ranasinghe PD, Linn S, Bass EB, Haythornthwaite JA. Meditation Programs for Psychological Stress and Well-being: A Systematic Review and Meta-analysis. *JAMA Intern Med*. 2014 174(3):357-68 (editorial by Gorroll. Moving towards Evidence Based Complementary Care)

42. Vu A, Adam A, Wirtz A, Pham K, Rubenstein L, Glass N, Beyrer C, **Singh S**. The Prevalence of Sexual Violence among Female Refugees in Complex Humanitarian Emergencies: a Systematic Review and Meta-analysis. *PLOS Currents Disasters.* 2014 Mar 18. Edition 1.

43. Wirtz AL, Pham K, Glass N, Loochkartt S, Kidane T, Cuspoca D, Rubenstein LS, **Singh S**, Vu A. Gender-based violence in conflict and displacement: qualitative findings from displaced women in Colombia. *Confl Health.* 2014; 8:10.

44. *Haar RJ, Footer KH, **Singh S**, Sherman SG, Branchini C, Sclar J, Clouse E, Rubenstein LS. Measurement of attacks and interferences with health care in conflict: validation of an incident-reporting tool for attacks on and interferences with health care in eastern Burma. *Conflict and Health.* 2014, 8:23.

45. Cavallazzi R, El-Kersh K, Abu-Atherah E, **Singh S**, Loke YK, Wiemken T, Ramirez J. Midregional proadrenomedullin for prognosis in community-acquired pneumonia: A systematic review. *Respir Med.* 2014 ;108(11):1569-1580.

46. Dorsey ER, Brocht AFD, Nichols PE, Darwin KC, Anderson KE, Beck CA, **Singh S**, Biglan KM, Shoulson I. Depressed mood and suicidality in individuals exposed to tetrabenazine in a large Huntington disease observational study. *Journal of Huntington's Disease* 2013; 2(4): 509-515.

47. Ter Riet G, Chesley P, Gross AG, Siebeling L, Muggensturm P, Heller N, Umbehr M, Vollenweider D, Yu T, Akl EA, Brewster L, Dekkers OM, Mühlhauser I, Richter B, **Singh S**, Goodman S, Puhan MA. All That Glitters Isn't Gold: A Survey on Acknowledgment of Limitations in Biomedical Studies. *PLoS One* 2013 ;8(11): e73623.

48. Wirtz AL, Glass N, Pham K, Rubenstein LS, **Singh S**, Vu A. Development of a screening tool to identify female survivors of gender-based violence in humanitarian settings: qualitative evidence from research among refugees in Ethiopia. *Conflict and Health* 2013, 7:13.

49. Loke YK, Ho R, Smith M, Wong O, Sandhu M, Sage W, **Singh S**. Systematic review evaluating cardiovascular events of the 5-alpha reductase inhibitor - Dutasteride. *J Clin Pharm Ther* 2013 38(5):405-15

50. Grosse Y, Loomis D, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Baan R, Mattock H, Straif K; International Agency for Research on Cancer Monograph Working Group. Collaborators: Stewart BW, Biggar RJ, Lachenmeier DW, **Singh S**, Tsuda H, Baguley B, Marques MM, Tseng CH, Knight TL, Beland FA, Betz JM, Carcache de Blanco EJ, Cunningham ML, Dunnick JK, Guo L, Jameson CW, Karagas M, Lunn RM, McCormick DL, Witt KL, Zhou S. Carcinogenicity of some drugs and herbal products. *Lancet Oncol*. 2013; 14(9):807-8.

51. Maruthur NM, **Joy S**, Dolan J, Segal JB, Shihab HM, Singh S. Systematic assessment of benefits and risks: study protocol for a multicriteria decision analysis using the Analytic Hierarchy Process for comparative effectiveness research. *F1000 Research*. 2013 Jul 24; 2:160

52. Loke YK, **Singh S**. Risk of acute urinary retention associated with inhaled anticholinergics in patients with chronic obstructive lung disease: systematic review. *Therapeutic Advances in Drug Safety* 2013, 4: 19-26.

53. **Singh S**, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Glucagonlike Peptide 1-Based Therapies and Risk of Hospitalization for Acute Pancreatitis in Type 2 Diabetes Mellitus: A Population-Based Matched Case-Control Study. *JAMA Intern Med* 2013 28; 173:1843-4. (editorial by Peter Butler in JAMA Internal Medicine and Edwin Gale in the BMJ)

54. **Singh S**, Chang HY, Richards TM, Weiner JP, Clark JM, Segal JB. Thiazolidinedione use and risk of hospitalization for pneumonia in Type 2 Diabetes Mellitus: A Population-Based Matched Case-Control Study. *F1000Research* 2013 2:145.

55. Brotman DJ, Shihab HM, Prakasa KR, Kebede S, Haut ER, Sharma R, Shermock K, Chelladurai C, **Singh S**, Segal JB. Pharmacological and Mechanical Strategies for Preventing Venous Thromboembolism after Bariatric Surgery: A Systematic Review and Meta-analysis. *JAMA Surg* 2013 148(7):675-86.

56. Kebede S, Prakasa KR, Shermock K, Shihab HM, Brotman DJ, Sharma R, Chelladurai Y, Haut ER, **Singh S**, Segal JB. A systematic review of venous thromboembolism in patients with renal insufficiency, obesity, or on antiplatelet agents. *J Hosp Med* 2013 ;8(7):394-401.

57. *Chelladurai Y, Stevens KA, Haut ER, Brotman DJ, Sharma S, Shermock KM, Kebede S**, Singh S**, Segal JB. Venous thromboembolism in patients with traumatic brain injury: a systematic review. *F1000Research* 2013. May 29; 2:132.

58. **Singh S**, Loke YK, Enright P, Furberg CD. The pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergics. *Thorax* 2013 68: 114-116.

59. Denizard-Thompson NR, **Singh S**, Stevens SR, Miller DP, Wofford JL. IPod™ technology for teaching patients about anticoagulation: a pilot study of mobile computer-assisted patient education. *Prim Health Care Res Dev* 2012 13: 42-7.

60. Treadwell JR, **Singh S**, Talati R, McPheeters ML, Reston JT. A Framework for "Best Evidence" Approaches in Systematic Reviews. *J Clin Epidemiol* 2012; 65: 1159-62.

61. Moore T, Glenmullen J, Maltsberger JT, Furberg CD, **Singh S**. Suicidal Behavior and Depression in Smoking Cessation Treatments. *PLOS One* 2011; 6: e27016.

62. Kwok CS, Yeong JK, Turner RM, Cavallazzi R, **Singh S**, Loke YK. Statins and associated risk of pneumonia: a systematic review and meta-analysis of observational studies. *Eur J Clin Pharmacol* 2012; 68(5): 747-55.

63. Moore T, **Singh S**, Furberg CD. The FDA and New Safety Warnings. *Archives of Internal Medicine* 2012 172:78-80.

64. Kwok CS, Arthur AK, Anibueze CI, **Singh S**, Cavallazzi R, Loke YK. Risk of Clostridium difficile Infection with Acid Suppressing Drugs and Antibiotics: Meta-Analysis. *Am J Gastroenterol* 2012; 107:1011-9 (with an editorial by Leontadis, Miller and Howden. How much do PPIs contribute to C difficile infection)

65. **Singh S,** Pant SB, Dhakal S, Pokhrel S, Mullany LC. Human Rights Violations among Sexual and Gender Minorities in Kathmandu, Nepal: A qualitative investigation. *BMC International Health and Human Rights* 2012, 12:7
66. **Singh S**, Chang SM, Matchar DB, Bass EB. Chapter 7. Grading a body of evidence on diagnostic tests. *J Gen Intern Med.* 2012; 27: S47-55.
67. Treadwell JR, Uhl S, Tipton K, Shamliyan T, Vishwanathan M, Berkman ND, Sun X, Coleman CI, Elshaug AG, **Singh S,** Wang SY, Ramakrishnan R. Assessing equivalence and noninferiority. *J Clin Epidemiol* 2012; 65: 1144-9.
68. **Singh S**, Loke YK. Drug Safety Assessment in Clinical Trials: Methodologic Challenges and Opportunities. *Trials* 2012, 13: 138.
69. Puhan M, **Singh S**, Varadhan R, Weiss C, Boyd CM. Methods for Benefit and Harm Assessment in Systematic Reviews. *BMC Medical Research and Methodology* 2012, 12: 173.
70. Mills EJ, Wu P, Chong G, Ghement I, **Singh S**, et al. Efficacy and safety of statin treatment for cardiovascular disease: a network meta-analysis of 170,255 patients from 76 randomized trials. *Q J Med* 2011; 104: 109-24.
71. **Singh S**, Loke YK, Furberg CD. Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: Systematic review and meta-analysis. *Thorax* 2011; 66: 383-388.
72. Bennett WL, Maruthur NM, **Singh S**, et al. Comparative effectiveness and safety of medications for Type 2 Diabetes: An update including new drugs and two drug combinations. *Annals of Internal Medicine* 2011; 154: 602-13. Copublished with linked AHRQ report:
73. Loke YK, Kwok CS, **Singh S**. Comparative Cardiovascular Effects of Thiazolidinediones: A systematic review and meta-analysis of observational studies. *BMJ* 2011; 342: d1309.
74. Loke YK, Cavallazi R, **Singh S**. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomized controlled trials and observational studies. *Thorax* 2011; 66: 699-708.
75. Miller DP Jr, Spangler JG, Case LD, Goff DC Jr, **Singh S**, Pignone M. Effectiveness of a Web-Based Colorectal Cancer Screening Patient Decision Aid: A Randomized Controlled Trial in a Mixed Literacy Population. *Am J Prev Med* 2011; 40: 608-15.
76. Li T, Puhan MA, Vedula SS, **Singh S**, et al. Network meta-analysis-highly attractive but more methodological research is needed. *BMC Medicine* 2011; 9: 79.
77. **Singh S**, Loke YK, Enright P, Furberg CD. Mortality Associated with Tiotropium Respimat® in Patients with Chronic Obstructive Pulmonary Disease- A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *BMJ* 2011; 342: d3215. (with an editorial by Chris Cates Safety of Tiotropium)
78. **Singh S**, Loke YK, Spangler JG, Furberg CD. Risk of serious adverse cardiovascular events with Varenicline: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *CMAJ* 2011; 1831359-66. (with an editorial by JT Hays. Varenicline for smoking cessation. Is it a heartbreaker?)

79. Loke YK, Kwok CS, **Singh S**. Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD: a systematic review and meta-analysis. *Eur Respir J* 2010; 35: 1003-1021.
80. Navaneethan S, **Singh S**, Appasamy S, et al. Sodium bicarbonate therapy for prevention of contrast-induced nephropathy- A systematic review and meta-analysis. *AJKD* 2009; 53: 617-627.
81. Loke YK, **Singh S**, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: Systematic Review. *CMAJ* 2009; 180: 32-39. (with an editorial by Lipscombe. Thiazolidinediones: Do harms outweigh benefits?)
82. **Singh S**, Amin A, * Loke YK. Long-term use of inhaled corticosteroids and risk of pneumonia in COPD: A meta-analysis. *Archives of Internal Medicine* 2009; 169: 219-229.
83. Attanayake V, Mckay R, Joffres M, **Singh S**, Burkle Jr F, Mills E. Prevalence of mental disorders among children exposed to war: a systematic review of 7920 children. *Medicine Conflict and Survival* 2009; 25: 4-19.
84. Loke YK, Jeevanantham V*, **Singh S**. Bisphosphonates and atrial fibrillation: systematic review and meta-analysis. *Drug Safety* 2009; 32: 219-228.
85. Boyd M, Watkins F, **Singh S**, Haponik E, Chatterjee A, Conforti J, Chin Jr R. Prevalence of flexible bronchoscopic removal of foreign bodies in the advanced elderly. *Age and Ageing* 2009; 38: 396-400.
86. Loke YK, Trivedi A, **Singh S**. Meta-analysis: Gastrointestinal bleeding due to interaction between Selective Serotonin Reuptake Inhibitors and Non-Steroidal Anti-inflammatory drug. *Alimentary Pharmacol Ther* 2008; 27: 31-40.
87. Mills E, **Singh S**, Roach B, Chong S. Prevalence of mental disorders and torture among Bhutanese refugees in Nepal: A systematic review and its policy implications. *Medicine, Conflict and Survival* 2008; 24: 5-16.
88. Chaukiyal P, Nautiyal A, Radhakrishnan S, **Singh S**, Navaneethan S. Thromboprophylaxis in cancer patients with central venous catheters: A systematic review and meta-analysis. *Thromb Haemost* 2008; 99: 38-43.
89. Wofford JL, Wells M, **Singh S**. Best Strategies for Patient Education Regarding Anticoagulation with Warfarin: A systematic review. *BMC Health Services Research* 2008; 8: 40.
90. Navaneethan SD, Adoulat S, **Singh S**. A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease. *BMC Nephrology* 2008;9: 3.
91. **Singh S**, Loke YK. Furberg CD. Inhaled anticholinergics and the risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *JAMA* 2008; 300: 1439-1450. (CME Article in JAMA)
92. Mills EJ, Checchi F, Orbinski JJ, Schull MJ, Burkle Jr FM, Beyrer C, Cooper C, Hardy C, **Singh S**, et al. Users' guides to the medical literature: how to use an article about mortality in a humanitarian emergency. *Confl Health* 2008; 30: 9.
93. **Singh S**, Kumar A. Wernicke encephalopathy after bariatric surgery: A systematic review. *Neurology* 2007; 68: 807-11.

94. **Singh S**, Sharma SP, Mills E, Poudel KC, Jimba M. Conflict Induced Internal Displacement in Nepal. *Medicine Conflict and Survival* 2007; 23: 103-110.

95. **Singh S**, Loke YK, Furberg CD. Thiazolidinediones and heart failure: A Teleo-Analysis. *Diabetes Care* 2007; 30: 2148-2153.

96. Beyrer C, Villar JC, Suwanvanichkij V, **Singh S**, Baral SD, Mills EJ. Neglected Diseases, Civil Conflicts and the Right to Health. *Lancet* 2007; 370: 619-627.

97. **Singh S**, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: A systematic review and meta-analysis. *JAMA* 2007; 298: 1189-1195. (with an editorial by DH Solomon and Winkelmeyer. Cardiovascular risk and the Thiazolidinediones déjà vu all over again?)

98. Mills EJ, **Singh S**. Health, Human Rights and the conduct of research within oppressed populations. *Global Health*. 2007; 3: 10.

99. Mills E Cooper C, Wu P, Rachlis B, **Singh S**, Guyatt GH. Randomized trials stopped early for harm in HIV/AIDS: A systematic survey. *HIV Clinical trials*; 2006; 7: 24-33.

100. Mills E, **Singh S**, Wilson K et al. The Challenges of involving traditional healers in HIV/AIDS care. *Int J STD & AIDS* 2006; 17: 360-363.

101. **Singh S**, Bøhler E, Dahal K, Mills E. The state of child health and human rights in Nepal. *PloS Med* 2006 3; 7: e203

102. Mills EJ, **Singh S**, Zwi A, Nelson B, Nachega JB. The impact of conflict on HIV/AIDS in Africa. *Int J STD AIDS* 2006; 17: 713-717.

103. Mills E, Nixon S, **Singh S**, Dolma S, Nayyar A, Kapoor S. Enrolling women into HIV vaccine trials: An ethical imperative but a logistical challenge. *PloS Med* 2006: 3: e94.

104. Dolma S, **Singh S**, Lohfield L, Orbinski J, Mills E. Dangerous Journey: Documenting the Experience of Tibetan Refugees. *AJPH* 2006; 96: 2061-2064.

105. Wofford JL, **Singh S**. Exploring the Educational Value of Clinical Vignettes from the SGIM National Meeting in the Internal Medicine Clerkship: A Pilot Study. *JGIM* 2006; 21: 1195-1197.

106. Navaneethan SD, **Singh S**. A systematic review of barriers in access to renal transplantation among African Americans in the United States. *Clin Transplant* 2006; 20: 769-775.

107. Mills E, Nachega JB, Buchan I, Attaran A, Orbinski J, **Singh S** et al. Adherence to Antiretroviral therapy in Africa versus North America: A comparative meta-analysis. *JAMA* 2006; 296: 679-690.

108. Mills E, Nachega JB, Bangsberg D, **Singh S**, Rachlis B, Wu P, et al. Adherence to antiretroviral therapy: a systematic review and meta-analysis examining developed and developing nation patient-reported barriers and facilitators. *PLoS Med* 2006; 3: e438.

109. **Singh S**, Loke YK. Statins and pancreatitis: A systematic review of observational studies and spontaneous case reports. *Drug Saf* 2006; 29: 1123-32.

110. **Singh S**, Mills E, Dahal K. Nepal's war on Human Rights: A summit higher than Everest. *Int J Equity Health*. 2005; 4: 9.

111. **Singh S**, Mills E. Honeyman SW, Suvedi BK, Pant NP. HIV in Nepal: Is the conflict fueling the epidemic? *PLoS Med*. 2005; 2: e 216.

112. Mills EJ, Rachlis B, Wu P, Wong E, Heise L Wilson K, **Singh S**. Media reporting of Tenofovir trials in Cambodia and Cameroon. *BMC International Health and Human Rights* 2005; 5: 6.

113. Mills E, **Singh S**, Holtz T, Santa-Barbara J, Chase R, and Orbinski J. Prevalence of serious mental disorders among Tibetan refugees: A systematic review. *BMC International Health and Human Rights* 2005; 5: 7.

114. **Singh S**, Dolan JG, Centor RM. Optimal clinical management of Sore throat: A multi-criteria decision analysis. *BMC Medical Decision-Making* 2005:6; 14.

Accepted

None

Books and monographs

1. **Singh S**, Fouyazi H, Anzuoni K, Goldman L, Min JY, Griffin M, Grijalva CG, Morrow JA, Whitmore C, Leonard CE, Selvan M, Nair V, Zhou Y, Toh S, Petrone A, Williams J, Fazio-Eynullayeva E, Swain R, Cole DT, Andrade S. Diagnostic algorithms for cardiovascular death in administrative claims databases. A systematic review 2018. Sentinel Report. Prepared for the Food and Drug Administration.
2. Some drugs and herbal products / IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2013: Lyon, France) (IARC monographs on the evaluation of carcinogenic risks to humans; volume 108). Published by the International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France ©International Agency for Research on Cancer, 2015 On-line publication, 15 September 2015.
3. Maruthur NM, Joy S, Dolan J, Segal JB, Shihab HM, **Singh S**. Systematic assessment of benefits and risks: A multicriteria decision analysis using the Analytic Hierarchy Process for comparative effectiveness research. FDA report 2013
4. Beyrer C, **Singh S**, Ambrosio M, Semini I. Revitalizing the HIV response in Pakistan: a systematic review and policy recommendations. World Bank, 2012.
5. Beyrer C, **Singh S**, Sudarshi D. Neglected tropical diseases, conflict and the right to health: A2, pgs 132- 155 in The Causes and Impacts of Neglected Tropical and Zoonotic Diseases: Opportunities for Integrated Intervention Strategies: Workshop Summary. Editors Eileen R. Choffnes and David A. Relman, Rapporteurs; Forum on Microbial Threats; Institute of Medicine ISBN 978-0-309.
6. Goyal M, **Singh S**, Sibinga EMS, Gould NF, Rowland-Seymour A, Sharma R, Berger Z, Sleicher D, Maron DD, Shihab HM, Ranasinghe PD, Linn S, Bass EB, Haythornthwaite JA. Meditation Programs for Psychological Stress and Well-being: Comparative Effectiveness Review No. 124 (Prepared by The Johns Hopkins University Evidence-based Practice Center, under Contract No. 290-2007-100061-1.) AHRQ Publication No. 13 (14)-EHC116-EF. Rockville, MD: Agency for Healthcare Research and Quality. January 2014
7. **Singh S**, Haut ER, Brotman DJ, Sharma R, Chelladurai Y, Shermock KM, Kebede S, Stevens KA, Prakasa KR, Shihab HM, Akande TO, Zeidan AM, Garcia LJ, Segal JB. Comparative Effectiveness of Pharmacologic and Mechanical Prophylaxis of Venous Thromboembolism Among Special Populations. Comparative Effectiveness Review No. 116. (Prepared by The

Johns Hopkins University Evidence-based Practice Center, under Contract No. HHSA 290 2007 10061 I). AHRQ Publication No. 13-EHC082-1 Rockville, MD: Agency for Healthcare Research and Quality. May 2013

8. Puhan MA, **Singh S**, Weiss CO, Varadhan R, Sharma R, Boyd CM. Evaluation of the Benefit and Harm of Aspirin for Primary Prevention of Cardiovascular Events: A Comparison of Quantitative Approaches. Methods Research Report. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I). AHRQ Publication No. 12(14)-EHC149-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2013.
9. Boyd CM, **Singh S**, Varadhan R, Weiss CO, Sharma R, Bass EB, Puhan MA. Methods for Benefit and Harm Assessment in Systematic Reviews. Methods Research Report. (Prepared by the Johns Hopkins University Evidence-based Practice Center under Contract No. 290-2007-10061-I). AHRQ Publication No. 12(13)-EHC150-EF. Rockville, MD: Agency for Healthcare Research and Quality; November 2012.
10. Treadwell JR, **Singh S**, Talati R, McPheeters ML, Reston JT. A Framework for "Best Evidence" Approaches in Systematic Reviews [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Jun. Report No: 11-EHC046-EF. AHRQ Methods for Effective Health Care.
11. Treadwell J, Uhl S, Tipton K, **Singh S**, Santaguida L, Sun X, Berkman N, Viswanathan M, Coleman C, Shamliyan T, Wang S, Ramakrishnan R, Elshaug A. Assessing Equivalence and Noninferiority. Methods Research Report. (Prepared by the EPC Workgroup under Contract No. 290-2007-10063.) AHRQ Publication No. 12-EHC045-EF. Rockville, MD: Agency for Healthcare Research and Quality, June 2012.
12. **Singh S**, Chang SM, Matchar DB, Bass EB. Grading a body of evidence on medical tests. AHRQ Publication No 12-EHC079-EF. Chapter 7 of the Methods Guide for Medical Test Reviews. 2012 (AHRQ Publication No 12-EHC017). Rockville, MD: Agency for Health Care Research and Quality; June 2012.
13. Bennett WL, Wilson LM, Bolen S, Maruthur N, **Singh S**, et al. Oral Diabetes Medications for Adults with Type 2 Diabetes. An Update. Comparative Effectiveness Review No. 27. (Prepared by Johns Hopkins Evidence-Based Practice Center under Contract No. 290-02-0018.) AHRQ Publication No. 11-EHC038. Rockville, MD: Agency for Healthcare Research and Quality, March 2011.
14. Khagendra Dahal* and **Sonal Singh**. "Primary Prevention-Acting on Human Rights in Nepal" in Peace Through Health; How health professionals can work for a less violent world" by Neil Arya & Joanna Santa Barbara. 187-188. @ 2008 Kumarian Press.

Editorials and other scholarly material in peer reviewed journals

1. **Singh S**. Nautiyal A. Fluoroquinolones increase the risk of aortic aneurysms and aortic dissection? *JACC* 2018: 72 (12): 1379-81
2. **Singh S.** The safety of generic prescription drugs in the United States. *Drug Safety* 2018; 45 (4):325-328.
3. **Singh S**. Valproate use during pregnancy was linked to autism spectrum disorder and childhood autism in offspring. *ACP Journal Club* 2013; 159: JC13-4.

4. **Singh S**. Segal JB. Thiazolidinediones and macular edema: Comment on Thiazolidinediones and macular edema in type 2 diabetes. *Archives of Internal Medicine*. 2012. 172: 1011-3.
5. **Singh S**. Furberg CD. Inhaled anticholinergics for chronic obstructive pulmonary disease: comment on "inhaled anticholinergic drug therapy and the risk of acute urinary retention in chronic obstructive pulmonary disease." *Archives of Internal Medicine* 2011; 171: 920-2.
6. **Singh S**. Daily use of Aspirin reduces long-term risk of death due to some cancers. *ACP Journal Club* 2011; 154: JC3-2.
7. **Singh S**, Furberg CD. Review: Calcium supplements increase risk of myocardial infarction. *Evid Based Med* 2010; 15: 181.
8. **Singh S**, Furberg CD. Thiazolidinediones and Cardiovascular Outcomes in Type 2 Diabetes. *Heart* 2009; 95: 1-3.
9. **Singh S**. Clinical Research in Emerging Countries. Third Annual Marcus Evans Conference *IDrugs* 2008; 11: 724-727.
10. **Singh S**, Trivedi A. Spontaneous reports as evidence of Adverse Drug Reactions. *South Med J*. 2008; 101: 16.
11. **Singh S**, Orbinski J, Mills EJ. Conflict and Health: A paradigm shift in global health and human rights. *Conflict and Health* 2007, 1: 1.
12. **Singh S**. Nautiyal A. Secondary hypertension due to drugs and toxins: A challenge for research on harm. *South Med J*. 2007; 100: 665-666.
13. **Singh S**. Hydralazine-induced lupus. *South Med J* 2006; 99: 6-7.
14. **Singh S**. Amiodarone-induced alveolar hemorrhage *South Med J* 2006; 99: 329-30.
15. **Singh S** Angiotensin-converting enzyme inhibitor-induced acute pancreatitis: in search of the evidence. *South Med J* 2006; 99: 1327-1328.
16. **Singh S**. Wooltorton E. Increased mortality among elderly patients with dementia using atypical antipsychotics. *CMAJ* 2005 173; 3: 252.
17. **Singh S**. The Stone Circle. *CMAJ* 2005; 172: 522.
18. **Singh S**. Tears from the Land of Snow: Health and Human Rights in Tibet. *Lancet* 2004; 364: 1009.

Publication of Educational Materials

Peer-reviewed educational publications

1. **Singh S**. Type 2 diabetes pharmacoepidemiology update 2014: safety versus efficacy. *Curr Diab Rep*. 2014; 14(12):563.
2. Chelladurai Y*, **Singh S**. Varenicline and cardiovascular events: a perspective review. *Therapeutic Advances in Drug Safety* 2014; 1-6: doi 10.1177/2042098614530421.
3. Beasley R, **Singh S**, Loke YK, Enright P, Furberg CD. Call for worldwide withdrawal of tiotropium Respimat mist inhaler. *BMJ* 2012; 345: e7390.
4. Loke YK, **Singh S**. Risks associated with tiotropium in chronic obstructive pulmonary disease: overview of the evidence to date. *Therapeutic Advances in Drug Safety* 2012; 3: 123–31

5. Cavalazzi R, **Singh S.** Inhaled corticosteroids in Chronic Obstructive Pulmonary Disease: How serious is the risk of pneumonia and should it impact use of ICS in COPD. *Current Infectious Disease Reports*. 2011; 13: 296-301.
6. Lexchin J, Arya N, **Singh S**. Gardasil – The New HPV Vaccine: The Right Product, the Right Time? A Commentary. *Healthcare Policy* 2010; 5: 26-36.
7. Cavalazzi R, **Singh S**. Inhaled corticosteroids in Chronic Obstructive Pulmonary Disease: How serious is the risk of pneumonia and should it impact use of ICS in COPD. *Current Infectious Disease Reports*. 2011; 13: 296-301.
8. **Singh S**, Loke YK. A critical analysis of the benefits and drawbacks of inhaled corticosteroids in chronic obstructive pulmonary disease. *International Journal of COPD* 2010; 5: 189-195.
9. **Singh S**, Loke YK. Risk of pneumonia associated with long-term use of inhaled corticosteroids in COPD: A critical review and update. *Current Opinion in Pulmonary Medicine* 2010; 16: 118-122
10. Mills EJ, Ford N, **Singh S**, Eyawo O. Providing Antiretroviral Care in Conflict Settings. *Current HIV/AIDS Report* 2009; 6: 201-9.
11. **Singh S**, Loke YK. Thiazolidinediones and cardiovascular disease- Balancing Benefit and Harm. *Geriatrics and Aging* 2008; 11: 29-35.
12. Orbinski J, Beyrer C, **Singh S**. Violations of human Rights: health practitioners as witnesses. *The Lancet* 2007; 370: 698-704.
13. **Singh S**, Morrell P. What caused Buddha's death? *Ars Medica* 2006; 79-84.
14. Mills EJ, Robinson J, Attaran A, Clarke M, **Singh S**, Upshur RE, Hermann KJ Jr, Yusuf S. Sharing evidence on humanitarian relief. *BMJ* 2005; 331: 1485-6.
15. Mills E, **Singh S**, Warren M, Orbinski J, Upshur RE. Designing research in vulnerable populations: lessons from HIV prevention trials that stopped early. *BMJ* 2005; 331: 1403-1406.
16. **Singh S**. Empathy: Lost or found in medical education? The Learning Curve *MedGenMed* 2005; 7: 3
17. **Singh S**. Impact of long-term political conflict on population health in Nepal. *CMAJ* 2004; 171: 1499-1501.

Peer reviewed Case Reports

1. *Chaukiyal P, **Singh S**, Woodlock T, Dolan JG, Bruner K. Intravascular large B cell lymphoma with multisystem involvement. *Leuk Lymphoma* 2006; 47: 1688-90.
2. Navaneethan SD, Kannan VS, Osowo A, Shrivastava R, **Singh S**. Concomitant intracranial aneurysm and carotid artery stenosis: A therapeutic dilemma. *South Med J*. 2006, 99: 757-8.
3. **Singh S**, Rajpal C, Nannapaneni S, Venkatesh S. Iopamidol myelography-induced seizures. *MedGenMed* 2005: 7: 11.
4. Nautiyal A, **Singh S**, Parmeswaran G, DiSalle M. Hepatic dysfunction in a patient with Plamodium vivax infection. *Med Gen Med* 2005: 7: 1.
5. Navaneethan SD, **Singh S**, Choudhry W. Nodular glomerulosclerosis in non-diabetic patients: Case report and literature review. *J Nephrol* 2005: 18: 613-615.
6. Nautiyal A, **Singh S**, DiSalle M, O'Sullivan J. Painful Horner syndrome as a silent harbinger of carotid dissection. *PloS Med* 2005; 80: 136-137.

7. **Singh S**, Nautiyal A, Dolan JG. Recurrent acute pancreatitis possibly induced by atorvastatin and rosuvastatin. Is statin-induced pancreatitis a class effect? *JOP* 2004; 5: 502-504.
8. **Singh S**, Srivastava R, Das V. Formulary Conversion Programs: The need for patient-specific risk assessment. *MedGenMed* 2004; 6: 28.

Correspondence

1. **Singh S**, Suchard MA. Pioglitazone Use and Risk of Bladder Cancer. *JAMA*. 2015 Dec 15; 314(23):2567-8.
2. **Singh S**, Loke YK, Furberg CD. Outpatient management of severe COPD. *NEJM* 2010; 363: 493.
3. **Singh S**, Loke YK. Inhaled corticosteroids: a controversial add-on treatment in COPD. *ERJ* 2010; 36:1-1.
4. **Singh S**, Loke YK, Furberg CD. Tiotropium in Chronic Obstructive Pulmonary Disease *NEJM* 2009; 360: 185-187.
5. Loke Y, **Singh S**. Inhaled Corticosteroids in Patients with Chronic Obstructive Pulmonary Disease. *JAMA* 2009; 301: 1432.
6. Toney JH, Fasick JI, **Singh S**, Beyrer C, Sullivan DJ Jr. Purposeful learning with drug repurposing. *Science* 2009; 325: 1339-40.
7. Serra A, Sechi G, **Singh S,** Kumar A. Wernicke encephalopathy after obesity surgery: a systematic review. *Neurology* 2007; 69: 615.
8. **Singh S**, Arya N, Mills E, Holtz T, Westberg G. Free medical students and doctors detained in Nepal. *Lancet* 2006; 367: 1730.
9. **Singh S**. Where next for China? Rising inequalities in health and wealth are greatest challenge. *BMJ* 2006; 333: 499.
10. Mills E, **Singh S**, Orbinski J, Burrows D. The HIV/AIDS epidemic in Cambodia, The *Lancet Infectious Diseases* 2005; 5: 596-597.
11. **Singh S**. Nautiyal A. Neurological complications of bariatric surgery. *Mayo Clinic Proceedings.* 2005; 80:134-137.
12. **Singh S**. Nepal's war and conflict-sensitive development. *PLOS Med*. 2005:2(1): e19.
13. **Singh S**, Dolan JG. Diagnosis and treatment of Group A pharyngitis strep. *Am Fam Physician*. 2005:71:1064.
14. **Singh S**. Drug-induced pancreatitis might be a class effect of statin drugs. *JOP* 2005; 6: 380.
15. **Singh S**. Special issue on South Asia: focus will be on Asia. *BMJ* 2004; 328: 288.
16. **Singh S**. Letter from the Himalayas. *CMAJ* 2004; 171:309-10.
17. **Singh S**. Post-traumatic stress in former Ugandan child soldiers. *Lancet* 2004; 63: 1648.
18. **Singh S**. Post-Immigrant Refugee Medicine: Children's needs should not be seen in isolation. *BMJ* 2004; 329: 742.
19. **Singh S**. Social and economic justice: the road to health. *CMAJ* 2004; 171: 1021.

Development of major curricular offerings.

2 credit Course for MD and MPH in comparative effectiveness research for the Johns Hopkins ICTR 2015-2016

Sonal Singh MD, MPH received his MD from Patna Medical College India (1999). He completed internal medicine residency training at Unity Health System, affiliate of Strong Memorial Hospital Rochester, NY. (American Board of Internal Medicine 2005) He obtained an MPH from Johns Hopkins Bloomberg School of Public Health (2008) and completed subsequent research training at the Johns Hopkins Hospital (2012) as a Junior Faculty Research Scholar supported by the National Institute of Health. He was the Associate Director for the Center for Drug Safety and core faculty Evidence Based Practice Center and the Center for Public Health and Human Rights at Johns Hopkins University. He has taught and held faculty appointments at Wake Forest University School of Medicine and Johns Hopkins University. He has received numerous awards including the Senior Scholarship Award from the Unity Health System (2005), Tinsley R Harrison Teaching Award for Education at Wake Forest University in 2007, Master Teacher Award at Wake Forest University (2008), Mid-Atlantic Society of General Internal Medicine Clinician Investigator of the Year Award (2010), the Bruce P Squires Award for the best research paper of the year from the Canadian Medical Association Journal (2011) and the third best student abstract award from the International Society of Pharmacoepidemiology (2013). He conducts clinical research with a focus on evidence synthesis, drug safety and shared decision making. Dr Singh has conducted research in several countries and has published more than 150 academic manuscripts to advance research and clinical care. His research efforts have been supported by the NIH, FDA, Agency for Health Care Research and Quality and the Patient Centered Outcome Institute and various private foundations. His research has been published in *Science, NEJM, Journal of the American Medical Association, Annals of Internal Medicine, Lancet and the British Medical Journal*, and featured in various outlets including Nature Medicine, NYTIMES, CNN, Washington Post and the Wall Street Journal. He currently serves on the editorial board of the *Evidence Based Medicine Journal* published by the BMJ, as a panel member of the American College of Chest Physician guideline writing group, and American College of Physicians Health Policy committee (Massachusetts chapter) He has served as a consultant to the World Bank, World Health Organization International Agency for Research Cancer, the Agency for Health Care Research and Quality, pharmaceutical sponsors and research firms and several non-governmental organizations. He is a practicing general internist with a passion for managing patients with complex medical conditions.

EXHIBIT B

Trial Testimony

I have not provided trial testimony.

Expert deposition (last 5 years)

1. US District Court of South Carolina, Charleston; *In Re Lipitor (Atorvastatin Calcium) marketing, sales practices and products liability litigation*, MDL No. 2:14-mn-02502-rmg, April 28, 2015; supplementary deposition, in 2016.
2. US States District Court, Eastern District Court of California; *Kristi Lauris Individually and as Successor in Interest to the Estate of Dainis Lauris; vs Defendants Novartis AG*, Case No. 1:16 cv 00393 –LJO-SAB. Case 2:17-cv-14302-RLR Document 49 Entered on FLSD Docket, 2017.
3. Circuit Court of Camden County, Missouri; *Grace Arlene Rahmoeller v. Walmart Stores, Inc. and Nicholas B. Collins*, Case No.: 15CM-CC00238, April 16, 2018.
4. US District Court, Southern District of Florida, *Dennis McWilliams and Lori McWilliams v. Novartis AG and Novartis Pharmaceuticals Corp.*, Case No. 17-14302, May 2, 2018.
5. *Mary Brufett and Jefferey Brufett, vs Iskra Pusic, MD, Keith E. Stocker Goldstein and Washington University*, Cause No 1622-CC01117 (Division 8), May 10, 2018.
6. US District Court Northern District of California, San Francisco Division; *In Re: Viagra (Sildenafil Citrate) and Cialis (Tadalafil) Products Liability Litigation*, Civil Case No.: 3:16-md-02691-RS, MDL No. 2691, August 9, 2018.

Exhibit 53

Prospective Study of Talc Use and Ovarian Cancer

Dorota M. Gertig, David J. Hunter, Daniel W. Cramer, Graham A. Colditz, Frank E. Speizer, Walter C. Willett, Susan E. Hankinson

Background: **Perineal talc use has been associated with an increased risk of ovarian cancer in a number of case–control studies; however, this association remains controversial because of limited supporting biologic evidence and the potential for recall bias or selection bias in case–control studies. In this study, we conducted a prospective analysis of perineal talc use and the risk of ovarian cancer. *Methods:* The Nurses' Health Study is a prospective study of 121 700 female registered nurses in the United States who were aged 30–55 years at enrollment in 1976. Talc use was ascertained in 1982 by use of a self-administered questionnaire: after exclusions, 78 630 women formed the cohort for analysis. Three hundred seven epithelial ovarian cancers subsequently diagnosed in this cohort through June 1, 1996, were confirmed by medical record review and met inclusion criteria. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs). *Results:* In 1982, 40.4% (n = 31 789) of the cohort reported ever using talc, and 14.5% (n = 11 411) reported ever using talc daily. We observed no overall association with ever talc use and epithelial ovarian cancer (multivariate RR = 1.09; 95% CI = 0.86–1.37) and no increase in risk of ovarian cancer with increasing frequency of use. There was a modest elevation in risk for ever talc use and invasive serous ovarian cancer (multivariate RR = 1.40; 95% CI = 1.02–1.91). The risk of epithelial ovarian cancer for talc users was not greater among women who had never had a tubal ligation (multivariate RR = 0.97; 95% CI = 0.71–1.32). *Conclusion:* Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancer. [J Natl Cancer Inst 2000;92:249–52]**

Talc was originally implicated as a possible ovarian carcinogen because of its chemical similarity to asbestos, which has been linked to ovarian cancer in occupational settings and is associated with mesotheliomas histologically resembling epithelial ovarian cancers *(1–3).* Perineal use of talcum powder has been positively associated with ovarian cancer risk in a number of case–control studies *(4–13),* although the magnitude of the associations has been modest, with odds ratios ranging from 1.2 to 1.9, and not all results reached statistical significance *(5,6,8).* Despite this relative consistency among studies, the limited supporting biologic evidence, together with the possibility of recall and selection bias in case–control studies *(1),* has raised questions about the plausibility of the association. We, therefore, prospectively examined the relationship between perineal talc use and ovarian cancer risk in a large cohort of U.S. women.

METHODS

The Nurses' Health Study, established in 1976, is a prospective cohort of 121 700 registered nurses living in 11 of the larger states in the United States. Questionnaires were mailed to married, female nurses aged 30–55 years, requesting information on health-related issues, including medical history and potential risk factors for cancer. Follow-up questionnaires have been mailed every 2 years to update information on exposures and to ascertain newly diagnosed diseases. The study was approved by the Human Research Committee at the Brigham and Women's Hospital, Boston, MA.

Ascertainment of cases. We sought medical records from all women who reported a diagnosis of ovarian cancer or who were deceased in each follow-up cycle. Records were reviewed by physicians unaware of exposure status. Histologic subtypes were determined from pathology reports, and epithelial ovarian cancers were classified as serous cancers (including cystadenocarcinoma and papillary adenocarcinoma), mucinous cancers (including adenocarcinoma and mucinous papillary adenocarcinoma), and endometrioid cancers (clear cell and other types, including mixed epithelial tumors). Borderline histologic tumors are included in the analysis. Deaths are reported by relatives and postal authorities, as well as a search of the National Death Index. Mortality follow-up is estimated to be 98% complete in this cohort *(14).* Cases of epithelial ovarian cancer (International Classification of Diseases Code, ICD183.0), confirmed by medical record review or death certificate, occurring between the return of the 1982 questionnaire and June 1, 1996, were included in the analysis.

Exclusions. Women who did not respond to the question on talc use in 1982 were excluded from this analysis. We also excluded women who had reported a diagnosis of cancer (other than nonmelanoma skin cancer) before 1982, as well as women who reported bilateral oophorectomy, surgery with an unknown number of ovaries removed, and a history of radiation therapy. Validity of self-reported surgical menopause has been assessed previously, and agreement with medical records was more than 97% *(15).* These exclusions were updated every 2 years. At baseline, 78 630 women were eligible for the analysis. The resulting population after exclusions contributed 984 212 person-years of follow-up and 307 cases of epithelial ovarian cancer.

Ascertainment of talc exposure. Use of talcum powder was ascertained on the 1982 questionnaire in the following ways: "Have you ever commonly used talcum, baby powder, or deodorizing powder *a*) to apply to perineal (private) area? No, daily, one to six times per week, or less than once per week or *b*) to apply on sanitary napkins? No, Yes." We classified "ever talc use" as ever talc use on either the perineal area or sanitary napkins.

Other covariates. Potential risk factors and confounders of the association between ovarian cancer and exposures of interest in this analysis also were obtained from the biennial questionnaires and were updated every 2 years where relevant. Oral contraceptive use was asked every 2 years from 1976 through 1982, by which time use was rare. Tubal ligation history was asked as part of a question on methods of contraception from 1976 through 1984, and, in 1994, women were asked if they had ever

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See "Notes" following "References."

had a tubal ligation and, if so, at what age. Family history of ovarian cancer was not asked until 1992. Parity was defined as the number of pregnancies lasting 6 months or more and was asked through 1984.

Statistical analysis. Incidence rates (number of cases for each category of exposure divided by person months of follow-up in that cycle) were calculated for each category, adjusting for age in 5-year intervals. Proportional hazards models by use of pooled logistic regression were used to derive relative risks (RRs) and 95% confidence intervals (CIs) of disease for each exposure category *(16)*. For age-adjusted analyses, we categorized variables as follows: parity (0, 1–2, or ⩾3), oral contraceptive use (never, past, or current), tubal ligation (yes or no), postmenopausal hormone use (never, past, or current), cigarette smoking (never, past, or current), and body mass index, i.e., weight in kilograms/height in meters squared (<21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2). In multivariate analyses, we adjusted for age (years) and for potential risk factors by use of indicator variables for each category as described above, except for parity (0, 1–2, 3–4, or ⩾5) and duration of oral contraceptive use (never or <3, 3–5, or >5 years), for which we used a larger number of categories to more appropriately control for confounding. In addition we controlled for age at menarche, duration of breast-feeding, and age at menopause. However, since this did not alter the estimates for talc use, further models did not control for these variables. Body mass index and duration of oral contraceptive use were also entered as continuous variables, and similar estimates were obtained. All RRs reported are multivariate unless otherwise stated. *P* values reported are two-sided.

RESULTS

Three hundred seven women developed ovarian cancer in the cohort from 1982 through 1996 who responded to the 1982 questionnaire on talc use. In 1982, 40.4% (n = 31 789) of the baseline cohort reported ever using talc, of which 14.5% (n = 11 411) were ever daily talc users. Talc use was associated with higher body mass index and inversely associated with current cigarette smoking (Table 1).

We did not observe an overall association with ever use of talc and epithelial ovarian cancer (RR = 1.09; 95% CI = 0.86–1.37). There was also no elevation in risk among daily users of perineal talc, and no trend was seen with increasing frequency of use (Table 2). Talc use on sanitary napkins was inversely related to ovarian cancer, but the association was statistically nonsignificant. Exclusion of use of talc on sanitary napkins from the ever use of talc variable did not substantially alter the results. We also evaluated the risk for women who used both perineal talc and talc on sanitary napkins but did not see an effect compared with never users of talc (RR = 0.90; 95% CI = 0.59–1.37).

When we stratified by histologic subtype, we observed a modest increase in risk for ever talc use for serous invasive cancers (RR = 1.40; 95% CI = 1.02–1.91) but not for all serous cancers (including borderline cancers), endometrioid cancers, or mucinous cancers (Table 3). For women who reported ever daily use of talc, the RR of invasive serous cancer was 1.49 (95% CI = 0.98–2.26). The RRs for ever talc users of less than once per week and one to six times per week were 1.29 (95% CI = 0.81–2.04) and 1.49 (95% CI = 0.77–2.11), respectively (*P* for trend = .05).

Table 1. Age-standardized prevalence of ovarian cancer risk factors according to perineal talc use in 1982*

	Ever perineal talc use, %† (n = 31 789)	No perineal talc use, % (n = 46 841)
Parity		
0	6.3	6.4
1–2	35.0	35.2
⩾3	58.7	58.4
Oral contraceptive use		
Current	0.5	0.6
Past	49.2	49.8
Never	50.4	49.6
Hormone use, postmenopausal women only		
Current	12.1	12.9
Past	20.5	20.4
Never	67.4	66.7
Tubal ligation, yes	17.6	17.6
Cigarette smoking		
Never	44.9	43.2
Past	30.3	28.3
Current	24.9	28.5
Body mass index quintiles, kg/m^2		
<21.0	16.0	22.1
21.0–22.9	20.9	25.4
23.0–24.9	20.1	20.6
25.0–28.9	22.8	19.6
⩾29	19.8	12.0

*Numbers do not always add up to 100% because of missing data or rounding.
†Ever talc use coded as either talc use on perineal area or talc use on sanitary napkins.

Table 2. Talc use and ovarian cancer: 1982 through 1996 (all subtypes included)*

	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
Talc use on perineum				
Never	186	608 020	1.0 (referent)	1.0 (referent)
<1/wk	43	128 923	1.10 (0.79–1.53)	1.14 (0.81–1.59)
1–6/wk	30	105 186	0.95 (0.65–1.40)	0.99 (0.67–1.46)
Daily	48	142 083	1.09 (0.79–1.49)	1.12 (0.82–1.55)
Talc use on sanitary napkins				
No	242	781 421	1.0 (referent)	1.0 (referent)
Yes	32	111 399	0.89 (0.62–1.29)	0.89 (0.61–1.28)
Ever perineal talc use				
No	179	586 758	1.0 (referent)	1.0 (referent)
Yes	128	397 454	1.05 (0.84–1.32)	1.09 (0.86–1.37)
Talc use, perineal and sanitary napkins				
None	179	586 758	1.0 (referent)	1.0 (referent)
Either talc use on perineum or use on sanitary napkins	103	307 317	1.11 (0.87–1.41)	1.15 (0.90–1.46)
Use on both sanitary napkins and perineum	25	90 137	0.89 (0.58–1.35)	0.90 (0.59–1.37)

*RR = relative risk; CI = confidence interval.
†Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ⩾5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Table 3. Talc use and ovarian cancer: 1982–1996 (by histologic subtype)*

Histologic subtype	No. of cases	Person-years	Age-adjusted RR (95% CI)	Multivariate RR† (95% CI)
All serous cancers, ever perineal talc use				
No	101	586 771	1.0 (referent)	1.0 (referent)
Yes	84	397 459	1.23 (0.92–1.64)	1.26 (0.94–1.69)‡
Serous invasive cancers, ever perineal talc use				
No	84	586 771	1.0 (referent)	1.0 (referent)
Yes	76	397 459	1.33 (0.98–1.82)	1.40 (1.02–1.91)‡
Endometrioid cancers, ever perineal talc use				
No	26	586 771	1.0 (referent)	1.0 (referent)
Yes	16	397 459	0.91 (0.49–1.69)	0.91 (0.49–1.87)
Mucinous cancers, ever perineal talc use				
No	30	586 771	1.0 (referent)	1.0 (referent)
Yes	20	397 459	0.98 (0.56–1.73)	0.93 (0.53–1.66)

*RR = relative risk; CI = confidence interval.

†Multivariate analyses controlling for age (years), parity (0, 1–2, or ⩾3), oral contraceptive use (never or ever), and tubal ligation history (yes or no).

‡Multivariate analyses control for age (years), parity (0, 1–2, 3–4, or ⩾5), duration of oral contraceptive use (never or <3 y, 3–5 y, or >5 y), body mass index (body weight in kilograms/height in meters squared: <21, 21.0–22.9, 23.0–24.9, 25.0–28.9, or ⩾29 kg/m^2), tubal ligation history (yes or no), smoking status (never, past, or current), and postmenopausal hormone use (never, past, or current).

Because the talc hypothesis depends on the ability of fibers to migrate up a patent genital tract to the ovaries, we evaluated the risk among women who had reported a tubal ligation and those who had not. Women who were ever talc users and had never had a tubal ligation were not at increased risk of epithelial ovarian cancer compared with women who had not used talc (RR = 0.97; 95% CI = 0.71–1.32). There was no evidence of heterogeneity of RRs between women who had a tubal ligation and women who did not. In addition, when women who had had a tubal ligation or simple hysterectomy were excluded from the analysis, the RR for ever talc use was 1.15 (95% CI = 0.89–1.49). For serous invasive cancers, the RR for women who had never had a tubal ligation was similar to that for women without a tubal ligation; however, the number of case patients who had had a tubal ligation was small (data not shown).

Cosmetic talc may have been more likely to contain asbestos fibers prior to 1976, before voluntary guidelines were proposed *(9).* As a proxy for early talc use, we assessed risk among women 45 years old or older in 1982. There was no evidence that older women in 1982 were at greater risk of ovarian cancer overall; the RR for ever talc use compared with never talc use for women under 45 years was 0.95 (95% CI = 0.59–1.53) and among women 45 years old or older was 1.13 (95% CI = 0.86–1.47). However, women 45 years old or older in 1982 who ever used talc had a higher risk of serous invasive cancer (RR = 1.51; 95% CI = 1.07–2.15). There was no evidence of effect modification by oral contraceptive use, body mass index, or cigarette smoking for epithelial cancers overall.

Discussion

To our knowledge, this is the first prospective analysis of talc use and ovarian cancer, and it addresses some of the potential limitations of previous case–control studies. Because we ascertained talc exposure prior to case diagnosis, the possibility for recall bias, which has been raised as a potential explanation for previous positive findings in case–control studies *(1),* is eliminated, and selection bias is reduced. We controlled for known or suspected ovarian cancer risk factors in the analysis, such as parity, oral contraceptive use, tubal ligation history, and body mass index, reducing the potential for uncontrolled confounding.

However, there are several important limitations to our study. The questions on talcum powder use referred to ever use, and we cannot determine the age at which women began using talc or the duration of use. Thus, we were unable to assess the potential effect of talc use before first pregnancy, which has been shown to be a stronger risk factor for ovarian cancer than use after pregnancy in one study *(13).* The number of lifetime applications of talc has also been associated with increased risk of ovarian cancer in some previous studies *(9,13).* Our relatively short follow-up period may be inadequate to detect an association if the latency for development of ovarian cancer is more than 15 years. Although we controlled for tubal ligation history, the tubal ligation question was asked as part of a question on contraceptive use; therefore, postmenopausal women and some premenopausal women who were not sexually active may not have responded to the question. Substantial residual confounding is unlikely, since there was no overall association between talc use and tubal ligation in this study. In addition, we excluded women who were postmenopausal in 1976 from analyses stratified by tubal ligation history. Finally, the prevalence of talc use in our study is somewhat higher than that in other studies and may reflect the fact that we asked about frequency of ever use rather than current regular use; this may have contributed to an attenuation of risk due to misclassification of exposure.

The potential effect of talc on the ovaries depends on migration of talc fibers through a patent genital tract, and we would, therefore, expect a stronger association among women without a tubal ligation who had used talc. However, no effect modification was seen by history of tubal ligation. Because we did not have the date of tubal ligation, some women may have begun talc use only after tubal ligation, potentially resulting in misclassification of talc use and attenuation of the RRs.

Since the first study showing an almost twofold increase in risk of ovarian cancer with any perineal talc use *(4),* most case–control studies have demonstrated positive associations with talc use *(4–13),* although not all have been statistically significant *(5,6,8).* Several studies *(9,17–20)* found no overall association between any genital talc use and ovarian cancer. We did not observe a dose–response relationship with talc use, and previous studies also have been inconsistent in this regard. Some studies *(9,13,17)* have demonstrated statistically insignificant trends in risk with increased frequency of talc use, duration of use, and measures of "total lifetime applications," while other studies *(6,8)* have not observed a statistically significant dose response.

With regard to histologic subtypes, a recent study by Cramer et al. *(13)* observed the greatest risk for talc use and invasive serous cancer; however, other

studies found increased risks for endometrioid cancers *(9,12)*, serous cancers *(7)*, and invasive cancers of all subtypes *(12)*. Since serous cancers, which account for more than half of all invasive ovarian cancers, most resemble mesotheliomas, it could be hypothesized that this subtype may be most likely associated with talc use. In our stratification by subtype, we did observe a modest positive association with serous invasive cancers and ever talc use as well as a borderline significant trend for increasing frequency of ever use.

The biologic evidence for the association of talc and ovarian cancer is incomplete. Asbestos has been linked to ovarian cancer in occupational settings and is associated with peritoneal tumors similar to ovarian cancer *(2,3,21)*. Because of the chemical similarity of talc and asbestos, talc also has been implicated as a possible ovarian carcinogen. Talc is able to migrate through the genital tract and gain access to the ovaries because talc fibers have been detected in benign and malignant ovarian tissue *(22)*, although no relation between reported levels of talc exposure and ovarian talc counts has been observed *(23)*. There have been few studies *(24,25)* of talc exposure in animals, and these studies have not demonstrated an increase in ovarian cancer among animals subjected to chronic talc exposure. These data should be interpreted cautiously because there are important anatomic and physiologic differences between rodents and humans, and talc in animals is often administered at high dose via aerosol exposure *(24)*.

In summary, we did not observe an overall association between epithelial ovarian cancer and ever use of talc, and there was no apparent dose response, although we lacked information on duration of talc use. In analyses stratified by histologic subtype, we observed a modest positive association between invasive serous cancer and ever talc use. Our results provide little support for any substantial association between perineal talc use and ovarian cancer risk overall; however, perineal talc use may modestly increase the risk of invasive serous ovarian cancers.

References

(1) Harlow BL, Hartge PA. A review of perineal talc exposure and risk of ovarian cancer. Regul Toxicol Pharmacol 1995;21:254–60.

(2) Keal E. Asbestosis and abdominal neoplasms. Lancet 1960;2:1211–6.

(3) Acheson ED, Gardner MJ, Pippard EC, Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocodilite asbestos: a 40 year follow-up. Br J Indust Med 1982;39:344–8.

(4) Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc: a case–control study. Cancer 1982;50:372–6.

(5) Chen Y, Wu PC, Lang JH, Ge WY, Hartge P, Brinton LA. Risk factors for epithelial ovarian cancer in Beijing, China. Int J Epidemiol 1992;21:23–9.

(6) Whittemore AS, Wu ML, Paffenbarger RS Jr, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. Am J Epidemiol 1988;128:1228–40.

(7) Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. Am J Epidemiol 1997;145:459–65.

(8) Booth M, Beral V, Smith P. Risk factors for ovarian cancer: a case–control study. Br J Cancer 1989;60:592–8.

(9) Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992;80:19–26.

(10) Purdie D, Green A, Bain C, Siskind V, Ward B, Hacker N, et al. Reproductive and other factors and risk of epithelial ovarian cancer: an Australian case–control study. Int J Cancer 1995;62:678–84.

(11) Shushan A, Paltiel O, Iscovich J, Elchalal U, Peretz T, Schenker J. Human menopausal gonadotropin and the risk of epithelial ovarian cancer. Fertil Steril 1996;65:13–8.

(12) Chang S, Risch HA. Perineal talc exposure and risk of ovarian carcinoma. Cancer 1997;79:2396–401.

(13) Cramer DW, Liberman RE, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.

(14) Stampfer MJ, Willett WC, Speizer FE, Sysert DC, Lipnick R, Rosner B, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837–9.

(15) Hankinson SE, Hunter DJ, Colditz GA, Willett WC, Stampfer MJ, Rosner B, et al. Tubal ligation, hysterectomy, and risk of ovarian cancer. JAMA 1993;270:2813–8.

(16) D'Agostino RB, Lee ML, Balanger AJ, Cupples LA, Anderson K, Kannel WB. Relation of pooled logistic regression to time dependent Cox regression analysis: the Framingham Heart Study. Stat Med 1990;9:1501–15.

(17) Hartge P, Hoover R, Lesher LP, McGowan L. Talc and ovarian cancer [letter]. JAMA 1983;250:1844.

(18) Rosenblatt KA, Thomas DB. Lactation and the risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Epidemiol 1993;22:192–7.

(19) Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer 1993;55:508–10.

(20) Wong C, Hempling RE, Piver MS, Natarajan N, Mettlin CJ. Perineal talc exposure and subsequent epithelial ovarian cancer: a case–control study. Obstet Gynecol 1999;93:372–6.

(21) Wignall BK, Fox AJ. Mortality of female gas mask assemblers. Br J Indust Med 1982;39:34–8.

(22) Henderson WJ, Joslin CC, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. J Obstet Gynecol 1971;78:266–72.

(23) Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol 1996;174:1507–10.

(24) Boorman GA, Seely JC. The lack of an ovarian effect of lifetime talc exposure in F344/N rats and B6C3F1 mice. Regul Toxicol Pharmacol 1995;21:242–3.

(25) Hamilton TC, Fox H, Buckley CH, Henderson WJ, Griffiths K. Effects of talc on the rat ovary. Br J Exp Pathol 1984;65:101–6.

Notes

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Exhibit 54

Int. J. Cancer: **81,** 351–356 (1999)

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Publication de l'Union Internationale Contre le Cancer

GENITAL TALC EXPOSURE AND RISK OF OVARIAN CANCER

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Epidemiologic studies have suggested an increased risk for ovarian cancer associated with the use of talcum powder in genital hygiene, but the biologic credibility of the association has been questioned. We conducted a population-based case-control study in eastern Massachusetts and New Hampshire involving 563 women with newly diagnosed epithelial ovarian cancer and 523 control women selected either by random digit dialing or through lists of residents. Use of body powders was assessed through personal interview and the exposure odds ratio (OR) for the use of talc in genital hygiene was calculated. Cases were more likely than controls (45% *vs.* 36%) to have used talc as a body powder in some manner, and the excess was confined to patients who used talc on the perineum directly or as a dusting powder to underwear or sanitary napkins. Relative to women who never used body powder or used it only in non-genital areas, the OR (and 95% confidence interval) associated with genital exposure to talc was 1.60 (1.18 and 2.15) after adjustment for age, study location, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. Exposure prior to rather than after a first livebirth appeared to be more harmful, and the association was most apparent for women with invasive serous cancers and least apparent for those with mucinous tumors. We conclude that there is a significant association between the use of talc in genital hygiene and risk of epithelial ovarian cancer that, when viewed in perspective of published data on this association, warrants more formal public health warnings. *Int. J. Cancer* 81:351–356, 1999.
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An association between the use of talc in genital hygiene and ovarian cancer was first examined in an epidemiologic study in 1982 (Cramer *et al.,* 1982). An elevated odds ratio for genital talc exposure was observed in this study, in 8 of the largest subsequent epidemiological studies (Whittemore *et al.,* 1988; Booth *et al.,* 1989; Harlow *et al.,* 1992; Chen *et al.,* 1992; Purdie *et al.,* 1995; Shushan *et al.,* 1996; Cook *et al.,* 1997; Chang and Risch, 1997) and in a study of borderline tumors (Harlow and Weiss, 1989). Only 3 smaller studies reported a null association (Hartge *et al.,* 1983; Rosenblatt *et al.,* 1992, Tzonou *et al.,* 1993). Despite this consistency, the association is still viewed with skepticism based upon weak odds ratios, poor dose-response relationships and an incomplete understanding of the biological mechanism by which talc might lead to ovarian cancer. We have completed a large population-based case-control study of ovarian cancer which offers new perspectives on the validity of the talc and ovarian cancer association.

MATERIAL AND METHODS

We conducted a population-based case-control study of women with newly diagnosed ovarian cancer who resided in eastern Massachusetts (MA) or New Hampshire (NH). Women with ovarian cancer were identified through hospital tumor boards and statewide cancer registries. Between 5/92 and 3/97, 1,080 cases of ovarian cancer were identified. After excluding 203 cases who had died or moved, had no telephone, did not speak English or had a non-ovarian primary tumor after review, 877 women remained eligible. Physicians denied permission to contact 126 (14%) of these women, and 136 cases (16%) declined to participate. Our analysis is based upon data from 563 cases with epithelial ovarian cancer, including those with tumors of borderline malignancy.

We identified control women using random digit dialing (RDD) in which the sampling unit for an interviewed case comprised the 99 telephone numbers generated from the first 5 digits of her telephone number plus all remaining combinations of the last 2 digits (excluding the case's own number). These numbers were listed in random order and called to screen households for potential controls who were within 4 years of the age of the case. Excluding business and non-working numbers, approximately 5,400 calls yielded 10% of households in which the household member declined to provide a household census and 80% of households in which an age and sex matched control for a case could not be made or a potential control was ineligible because of a prior oophorectomy. Of the remaining 10% of households screened with a potential eligible control, 72% agreed to participate. RDD proved inefficient for identifying controls over age 60 in MA since a substantially greater number of households needed to be screened to obtain an older control. Except in NH where complete listings of residents were unavailable, we chose to identify older controls in MA by randomly selecting women through use of lists (townbooks) of all residents in towns by name, age, and address according to precinct. We matched older controls to cases by community and age within 4 years based on the townbooks. Of 328 sampled townbook controls, 21% could not be reached, 18% were ineligible and 30% declined to participate. This analysis includes a total of 523 RDD and townbook controls.

In introducing the study to potential cases and controls, specific hypotheses including the talc association were not discussed. After written informed consent, we assessed demographic information, menstrual and reproductive history, medical and family history and personal habits using an in-person interview. We assessed exposures occurring prior to a "reference date," defined as 1 year before the date of diagnosis for cases and the date of interview for controls. We asked whether women had "regularly used talc, baby, or deodorizing powders dusted or sprayed" to feet, arms or other non-genital areas, to the genital or rectal area, on sanitary napkins, or on underwear, with the latter 3 methods defined as "genital exposure" and either no use or use in non-genital areas defined as "no genital exposure." A husband's use of powder in his genital area was also assessed. Age at first use, types of powder(s) used, applications per month and total years of use in genital hygiene were assessed in talc users. We did not assess potential talc exposure from diaphragms or condoms, exposures not found to be associated with ovarian cancer in our previous studies (Cramer *et al.,* 1982; Harlow *et al.,* 1992).

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TABLE I – PERINEAL TALC EXPOSURE[1] IN RELATION TO OVARIAN CANCER RISK BY CHARACTERISTICS OF STUDY PARTICIPANTS

	Cases		Controls		Age-adjusted[2] OR	(95% C.I.)
	Total	Talc exposure (%)	Total	Talc exposure (%)		
Age						
<50	266	66 (24.8)	262	43 (16.4)	1.68	(1.09, 2.58)
≥50	297	86 (29.0)	261	52 (19.9)	1.64	(1.11, 2.43)
Study center						
MA	433	126 (29.1)	411	85 (20.7)	1.56	(1.14, 2.14)
NH	130	26 (20.0)	112	10 (8.9)	2.49	(1.14, 5.45)
Education						
≤12	218	58 (26.6)	171	28 (16.4)	1.79	(1.08, 2.97)
>12	344	93 (27.0)	352	67 (19.0)	1.59	(1.10, 2.27)
Marital status						
Never married	110	31 (28.2)	61	10 (16.4)	1.77	(0.78, 4.00)
Ever married	453	121 (26.7)	462	85 (18.4)	1.62	(1.18, 2.22)
Religion						
Jewish	54	18 (33.3)	44	10 (22.7)	1.69	(0.68, 4.18)
Non-Jewish	509	134 (26.3)	479	85 (17.8)	1.63	(1.20, 2.22)
Weight						
<140	237	57 (24.0)	247	40 (16.2)	1.60	(1.02, 2.53)
≥140	326	95 (29.1)	275	55 (20.0)	1.65	(1.13, 2.42)
Use of OCs (months)						
<3 or never	334	98 (29.3)	247	52 (21.0)	1.55	(1.06, 2.28)
≥3	229	54 (23.6)	276	43 (15.6)	1.67	(1.07, 2.61)
Number of liveborn children						
0	185	55 (29.7)	106	20 (18.9)	1.65	(0.92, 2.98)
1–2	212	49 (23.1)	209	34 (16.3)	1.56	(0.95, 2.54)
3+	166	48 (28.9)	208	41 (19.7)	1.69	(1.04, 2.75)
Prior tubal ligation						
No	488	135 (27.7)	437	76 (17.4)	1.80	(1.31, 2.47)
Yes	75	17 (22.7)	86	19 (22.1)	0.98	(0.46, 2.08)
Prior hysterectomy						
No	529	139 (26.3)	487	88 (18.1)	1.60	(1.18, 2.16)
Yes[3]	34	13 (38.2)	36	7 (19.4)	2.61	(0.88, 7.78)
Family history of breast or ovarian cancer						
No	481	132 (27.4)	462	87 (18.8)	1.59	(1.17, 2.17)
Yes	82	20 (24.4)	61	8 (13.1)	2.21	(0.89, 5.48)

OR: odds ratio; CI: confidence interval; OCs: oral contraceptives.–[1]Sources of perineal talc exposure include dusting of underwear, diaphragms, sanitary napkins and/or dusting of genital area.–[2]Adjusted for age as a continuous variable.–[3]Excludes those with tubal ligation prior to hysterectomy.

For all cases studied, we reviewed pathology reports and sought slides in any instance where there was a discrepancy between histologic description and final diagnosis. After completing the review, cases were grouped according to the following histologic categories: serous cancers (including serous cystadenocarcinomas and surface papillary carcinomas), mucinous cancers, endometrioid and clear cell cancers, including mixed mesodermal or mixed epithelial with an endometrioid or clear cell component) and undifferentiated or other cancers. According to Young *et al.* (1994), serous tumors tend to be either borderline or invasive and seldom display a mixture while borderline and invasive grades often intermingle within other histologic types, especially the mucinous tumors. Based on this tendency, only serous borderline tumors were distinguished from invasive cancers when considering odds ratios by histologic type and grade.

Since matching was performed as the most convenient means for selecting controls comparable to cases in age and geographic locale and not as the principal means of controlling for confounding, matching was not preserved in the analysis. We analyzed our data by constructing frequency counts of cases and controls by study variables and by calculating crude odds ratios (OR). We then used unconditional logistic regression to adjust for the matching variables including age (continuous), study site (MA, NH), body mass index (continuous), which might have influenced likelihood of using body powder, and for variables strongly linked to ovarian cancer risk such as parity (0, 1), oral contraceptive use (never or <3 months, ≥3 months) and family history of breast or ovarian cancer (no, yes) and tubal ligation (no, yes). Most analyses were performed by using the SAS system (SAS Institute, Cary, NC). Tests for linear trend were performed using the likelihood ratio test with continuous forms of the talc variables. Frequency counts from studies included in our review of published studies were entered into STATA (College Station, TX) to compute crude and combined odds ratios.

RESULTS

Table I summarizes data regarding how cases and controls differed demographically and by known risk factors for ovarian cancer, how these same variables influenced genital talc exposure among controls and how the association between talc use in the genital area and ovarian cancer varied among strata. Controls were more likely than cases to have gone beyond high school, to have married, to have had children and to have used oral contraceptives. In examining the frequency of talc use among controls, only study location significantly influenced likelihood of genital talc exposure. Women from New Hampshire were less likely to have used talc in the genital area compared to women from Massachusetts. Ovarian cancer cases in almost all strata were more likely to have used powder genitally compared to controls, with corresponding elevated odds ratios. A notable exception was the lack of an association between talc use and ovarian cancer among women who reported having had a tubal ligation.

Table II shows adjusted odds ratios by manner, type and frequency of powder use. A greater percentage of cases had regularly used powder in some manner compared to the controls.

TABLE II – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH TYPES AND FREQUENCY OF POWDER USE

Type of personal use	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No personal use	312 (55.4)	334 (63.9)	1.0	
Use, non-genital areas	99 (17.6)	94 (18.0)	1.08	(0.77, 1.50)
Use, dusting perineum	71 (12.6)	51 (9.8)	1.45	(0.97, 2.18)
Use, dusting sanitary napkin	20 (3.6)	12 (2.3)	1.45	(0.68, 3.09)
Use, dusting underwear	8 (1.4)	6 (1.2)	1.21	(0.40, 3.64)
Multiple uses genital area	53 (9.4)	26 (5.0)	2.15	(1.30, 3.57)
Genital use				
No personal genital exposure	411 (73.0)	428 (81.8)	1.0	
Any personal genital exposure	152 (27.0)	95 (18.2)	1.60	(1.18, 2.15)
Longest used type of powder[2]				
No genital use	411 (73.4)	428 (81.8)	1.0	
Talc	148 (26.4)	92 (17.6)	1.69	(1.26, 2.27)
Cornstarch	1 (0.2)	3 (0.6)	0.31	(0.03, 3.01)
Husband use[3,1]				
No	291 (87.6)	346 (92.0)	1.0	
Yes	41 (12.4)	30 (8.00)	1.52	(0.92, 2.52)
Frequency of use per month[4]				
<30	64 (11.5)	28 (5.4)	2.21	(1.37, 3.56)
30–39	59 (10.6)	51 (9.8)	1.17	(0.78, 1.76)
40+	23 (9.8)	15 (2.9)	1.57	(0.80, 3.10)

[1]Adjusted for age (continuous), study center (MA, NH), tubal ligation (ever, never), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months), and primary relative with breast or ovarian cancer (yes, no) and other categories of genital talc use, except where noted.–[2]Adjusted for age (continuous), study center (MA, NH), and tubal ligation (ever, never) and other powder.–[3]Among married women with no personal genital talc use.–[4]Total of all uses in the genital area.

Relative to those with no use of a body powder, those who used powder only in non-genital areas did not have an increased risk of ovarian cancer [OR=1.08 (0.77 and 1.50)]. However, elevated ORs and (95% CI) were observed for women who directly powdered the genital or rectal area [1.45 (0.97 and 2.18)]; who dusted sanitary napkins: 1.45 (0.68 and 3.09); who dusted underwear [1.21 (0.40 and 3.64)] and who used powder in multiple ways in the genital area [2.15 (1.30 and 3.57)]. There was a significant excess of cases who regularly used powder in some manner in the genital area, and the adjusted OR was similar whether the non exposed referent group was considered to be women with no use of talc anywhere [OR= 1.58, (1.16 and 2.16)] or women with no genital use including those who used it as a body powder in non-genital areas [OR= 1.60 (1.18 and 2.15)]. Few of the women in our study reported use of cornstarch rather than a talc-based powder leading to an imprecise and non-significant OR for ovarian cancer risk associated with its use in the genital area. Among married women who never personally used talc in the genital area, there was an increase of borderline significance in ovarian cancer risk for women whose husbands had used talc in their genital area [OR=1.52 (0.92, 2.52)]. When we examined all methods of genital talc use (except exposure from a husband), we found that most of those who used talc had 30 or more applications per month, but there was no apparent trend for increasing risk for ovarian cancer with increasing number of monthly applications.

Table III examines risk for ovarian cancer associated with ordinal categories related to duration or intensity of talc exposure in the genital area relative to women who never used talc or who used it only in non-genital areas. No clear linear trend was apparent in ORs for categories of age at first use, years of use or total applications. To examine dose response, each of these variables was used as a continuous variable in multivariate models. Linear trends were significant only in those models that included women who were not exposed. To duplicate an analysis performed in a previous report (Harlow *et al.*, 1992), we examined total applications censored by excluding use after closure of the female tract or during non-ovulatory years. Although the ORs for the categories displayed a trend, once again only the multivariate model including the non-genitally exposed revealed a significant trend.

Table IV presents a more detailed analysis of the effect of genital use of talc in women who had no pregnancies at all, in women who had a pregnancy not resulting in a liveborn and in women with a liveborn pregnancy. In the latter 2 groups, we examined risk for ovarian cancer with the timing of talc use in relation to the first pregnancy. Genital talc use that began after a first pregnancy appeared to be associated with lower risk compared to use which began before the first pregnancy. The effect was more apparent among those with a liveborn. Eighty-five of 374 parous cases used at least some talc prior to their first liveborn compared to 64 of 416 parous controls, leading to an adjusted OR (95% CI) of 1.58 (1.10 and 2.29). In contrast, 8 of 378 parous cases used talc only after their first livebirth compared to 10 of 417 parous controls, leading to an adjusted OR(95% CI) of 0.97 (0.38 and 2.50) for ovarian cancer associated with talc use after a first livebirth.

Table V shows the average age and use of genital talc for all controls and for cases by histologic type of ovarian cancer. Average age differed by histologic type but did not account for the differences in ORs. The odd ratio for genital talc use was greatest (and significant) for invasive serous tumors and less than 1 only for mucinous tumors (invasive and borderline combined) after adjustment for age and other covariates.

DISCUSSION

Consistent with four recent case-control studies of ovarian cancer (Purdie *et al.*, 1995, Sushan *et al.*, 1996, Cook *et al.*, 1997, Chang and Risch, 1997), our results demonstrate a significant association between the use of talc in genital hygiene and risk for ovarian cancer. In our discussion, we will examine whether this association satisfies traditional criteria for a causal association including consistency and strength of the association, potential biases, dose response and biological credibility.

Figure 1 summarizes data on risk for ovarian cancer with any genital use of talc from 14 case-control studies including this one. The combined odds ratio and 95% CI is 1.36 (1.24 and 1.49), which is statistically significant. Odds ratios deviating most from the pooled value were observed in the smaller studies, and the test for heterogeneity was not significant (p=0.085). Thus, the criteria for

TABLE III – ADJUSTED ODDS RATIOS FOR OVARIAN CANCER ASSOCIATED WITH GENITAL USE OF TALC

Type of exposure	Cases Number (%)	Controls Number (%)	Adjusted OR[1]	(95% C.I.)
No genital use	411 (73.0)	428 (81.8)	1.0	
Age at first use				
<20	97 (17.4)	67 (12.8)	1.46	(1.03, 2.07)
20–25	36 (6.5)	18 (3.4)	1.87	(1.03, 3.39)
>25	13 (2.3)	9 (1.7)	1.54	(0.64, 3.72)
p-value for linear trend is 0.504 excluding non-exposed.				
Years of use				
<20	55 (9.9)	31 (5.9)	1.86	(1.16, 3.00)
20–30	32 (5.8)	26 (5.0)	1.33	(0.76, 2.30)
>30	59 (10.6)	37 (7.1)	1.44	(0.91, 2.26)
p-value for linear trend is 0.477 excluding non-genitally exposed and 0.062 including non-genitally exposed.				
Total applications				
<3000	51 (9.2)	27 (5.2)	1.84	(1.12, 3.03)
3000–10,000	36 (6.5)	28 (5.4)	1.43	(0.84, 2.41)
>10,000	59 (10.6)	39 (7.5)	1.43	(0.92, 2.22)
p-value for linear trend is 0.164 excluding non-genitally exposed and 0.472 including non-genitally exposed.				
Applications censored[2]				
<3000	59 (10.6)	41 (7.8)	1.54	(1.01, 2.35)
3000–10,000	51 (9.2)	31 (5.9)	1.72	(1.08, 2.76)
>10,000	36 (6.5)	20 (3.8)	1.80	(1.02, 3.18)
p-value for linear trend is 0.675 excluding non-genitally exposed and 0.022 including non-genitally exposed.				

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no), parity (0, ≥1), OC use (<3 months, ≥3 months), tubal ligation, and other categories of genital talc use, except where noted.–[2]Excludes applications following hysterectomy or tubal ligation and applications during pregnancy and periods of OC use. Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).

TABLE IV – EVER USE OF TALC IN THE GENITAL AREA IN RELATION TO PREGNANCY AND CHILDBIRTH

Group	Cases Total	Cases Number exposed	(%) exposed	Controls Total	Controls Number exposed	(%) exposed	Adjusted OR	95% C.I.
Nulligravid[1]	145	42	(29.0)	82	17	(20.7)	1.48	(0.76, 2.86)
Nulliparous[1] prior to first pregnancy	40	13	(32.5)	24	3	(12.5)	2.80	(0.64, 12.20)
Nulliparous[1] only after first pregnancy	40	2	(5.0)	24	1	(4.2)	1.24	(0.10, 15.32)
Parous[1] prior to first livebirth	374	85	(22.7)	416	64	(15.4)	1.58	(1.10, 2.29)
Parous[2] only after first livebirth	378	8	(2.12)	417	10	(2.40)	0.97	(0.38, 2.50)

[1]Adjusted for age (continuous), study center (MA, NH), BMI (continuous) and primary relative with breast or ovarian cancer (yes, no).–[2]Adjusted for age (continuous), study center (MA, NH), BMI (continuous), primary relative with breast or ovarian cancer (yes, no) and tubal ligation.

TABLE V – HISTORY OF GENITAL TALC USE AND ASSOCIATED ODDS RATIOS BY HISTOLOGIC TYPE AND GRADE

Histologic type/grade	Total	Average age	Any use of genital talc	No use of genital talc	Adjusted OR[1]	(95% CI)
Controls	523	49.3	95	428	1.0	
Histologic type/grade						
Serous borderline	86	41.8	23	63	1.38	(0.82, 2.31)
Serous invasive	229	54.5	72	157	1.70	(1.22, 2.39)
Mucinous	83	46.7	16	67	0.79	(0.44, 1.40)
Endometrioid/clear cell	130	53.9	31	99	1.04	(0.67, 1.61)
Undifferentiated	35	52.9	10	25	1.44	(0.67, 3.08)

[1]Adjusted for age (continuous), study center (MA, NH), primary relative with breast or ovarian cancer (yes, no), BMI (continuous), parity (0, ≥1), OC use (<3 months, ≥3 months) and tubal ligation (ever, never).

consistency of the association appear to be satisfied. A summary odds ratio of 1.36 suggests that between 10 and 11% of ovarian cancers in these populations are attributable to the genital use of talc depending upon whether the average control exposure of 36% or average case exposure of 43% is considered.

Despite the consistency noted above, the relatively weak odds ratios observed could reflect potential biases, especially recall and confounding. Recall bias is possible because talc exposure in these studies is based on personal recollection. However, recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias. Furthermore, if publicity regarding the association correlated with selective recall, one might expect a trend for cases from more recent studies to report higher

Risk of ovarian cancer with perineal exposure to talc from key epidemiologic studies.

Author	Cases Total n	Cases Exposed (%)	Controls Total n	Controls Exposed (%)	Crude OR (95% CI)
Cramer *et al.* (1982)	215	(42.8)	215	(28.4)	1.9 (1.3-2.8)
Hartge *et al.* (1983)	135	(49.6)	171	(58.5)	0.7 (0.4-1.1)
Whittemore *et al.* (1988)	188	(52.1)	539	(46.0)	1.3 (0.9-1.8)
Harlow and Weiss (1989)	116	(42.2)	158	(40.5)	1.1 (0.7-1.7)
Booth *et al.* (1989)	217	(65.0)	434	(59.0)	1.3 (0.9-1.8)
Harlow *et al.* (1992)	235	(48.5)	239	(39.3)	1.4 (1.0-2.1)
Rosenblatt *et al.* (1992)	77	(87.0)	46	(88.0)	1.0 (0.3-3.0)
Chen *et al.* (1992)	112	(6.2)	224	(2.2)	2.9 (0.9-9.4)
Tzonou *et al.* (1993)	189	(3.2)	200	(3.5)	0.9 (0.3-2.7)
Purdie *et al.* (1995)	824	(56.7)	860	(52.0)	1.2 (1.0-1.5)
Shushan *et al.* (1996)	200	(10.5)	408	(5.6)	2.0 (1.0-3.6)
Cook *et al.* (1997)	313	(50.8)	422	(39.3)	1.6 (1.2-2.1)
Chang and Rish (1997)	450	(44.0)	564	(35.6)	1.4 (1.1-1.8)
Cramer *et al.* (1999)	563	(27.0)	528	(18.2)	1.7 (1.2-2.2)
Summary odds ratio (95% confidence interval)					1.4 (1.2-1.5)

Odds ratios and confidence intervals

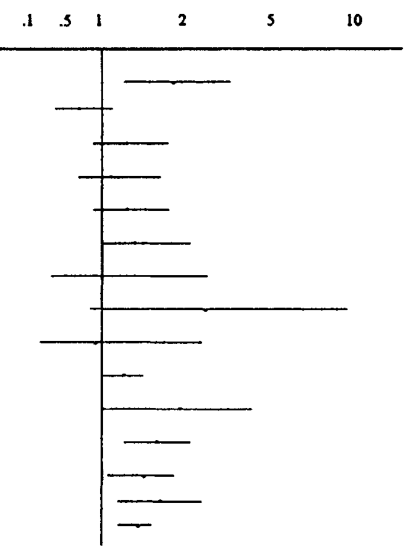

FIGURE 1 – Exposure rates, crude odds ratios and confidence intervals for case-control studies of genital talc use and ovarian cancer.

exposure rates, but the exposure rates noted in Figure 1 do not suggest this is the case. It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer which appears not to be the case from Table V. Our study found the greatest risk to be associated with invasive serous tumors, OR=1.70 (1.22 and 2.39). Cook *et al.* (1997) found talc use to be most strongly associated with serous and unclassified cancers, although Chang and Risch (1997) found endometrioid cancers to be more strongly linked with talc use.

Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or OC use and little variability of the association by these and other variables (Table II). Chang and Risch (1997) adjusted for age, parity, breastfeeding, oral contraceptive use, tubal ligation or hysterectomy and family history and also found the association to persist. Characteristics such as body odor or excessive perspiration might represent subtle constitutional features that might predispose to both talc use and ovarian cancer, but adjusting for BMI should control for these effects. In addition, 2 previous studies (Cook *et al.*, 1997; Chang and Risch, 1997), and our current study found no evidence of elevated risk associated with genital use of a cornstarch based-powder, although in all of these studies the exposure was infrequent and the OR and confidence interval was wide. Further studies would be valuable since this observation suggests that type of powder used may be more important than underlying reason for use.

The most obvious weakness in the argument for biologic credibility of the talc and ovarian cancer association is the lack of a clear dose response. Most talc and ovarian cancer studies that have addressed dose response, including this one, have failed to demonstrate consistent dose response relationships with measures of the intensity of the exposure, especially when the trend is examined among users only. In attempting to address this weakness, we point out that it is difficult to quantify the amount of powder actually used and degree of perineal dusting that might constitute an "application of talc." Another factor that may affect the dose-response relationship is whether use occurred at a time when the female tract was open. There is evidence from several studies that the talc/ovarian cancer association is modified by closure of the female tract as a result of tubal ligation or hysterectomy (Harlow *et al.*, 1992; Chang and Risch, 1997; Green *et al.*, 1997). We have also proposed that talc use during periods of ovulation may carry greater risk, based on the hypothesis that ovarian surface epithelial disruption and repair accompanying ovulation might allow talc to become entrapped within the inclusion cysts that form with ovulation.

Our current study also suggests that a term pregnancy may affect the relationship between talc and ovarian cancer in a manner that may be independent of ovulation. We observed that the association between talc and ovarian cancer was more apparent in women who used talc prior to a first liveborn pregnancy compared to those who used it only after a first liveborn pregnancy. This may suggest that ovarian tissue that has not (yet) gone through a pregnancy may be more susceptible to talc-induced damage than tissue that has undergone a pregnancy. A possible biologic explanation for this may involve an ovarian change, known as decidual reaction, that occurs during pregnancy. The decidual reaction refers to differentiation of stromal cells that occurs primarily in the endometrium of the pregnant uterus but which also may be seen in the fallopian tubes, pelvic peritoneum and ovarian surface (Herr *et al.*, 1978). Studies to determine whether the decidual reaction alters the susceptibility of ovaries (or pelvic peritoneum) to talc-induced damage may be informative.

Although we do not know precisely how use of talc in the genital area might induce ovarian cancer, some key elements supporting the biologic plausibility of the association have been established. It has been demonstrated that inert particles contaminating the vagina can reach the ovaries (Venter and Iturralde, 1979). Talc has been found in both normal and malignant ovarian tissue (Henderson *et al.*, 1979), although Heller *et al.* (1996) reported a poor correlation between the amount of talc in the ovaries and personal history of talc use. The patency of the female tract and the nature of ovarian cancer as a surface epithelial (mesothelial) lesion make the ovary a target for foreign body carcinogenesis. Indeed, human ovarian cancer has been demonstrated to be a consequence of occupational asbestos exposure (Keal, 1960). Talc, as a chemical relative of asbestos, appears able to induce histologic changes that are similar to those of asbestos, at least in the lungs (Kleinfeld et al., 1967). Biologic credibility for an association would be strengthened by an animal model, but an experiment capturing all of the potential factors in the human "model" would be very difficult. These elements include chronicity of the exposure, anatomic and physiologic uniqueness of women, effects of pregnancy and potential spread through coitus (as suggested by our finding related to ovarian cancer risk associated with a husband's use of talc). Rodent models seem poorly suited to address these issues because of their infrequent ovulation and the fact that the rodent ovary is encased in a bursal sac.

In summary, we have demonstrated a consistent association between talc and ovarian cancer that appears unlikely to be explained by recall or confounding. The dose-response relationship is weak but improved by considering factors such as closure of the female tract, ovulation and exposure prior to pregnancy, and we have outlined a plausible biologic rationale for this association. We estimate that avoidance of talc in genital hygiene might reduce the occurrence of a highly lethal form of cancer by at least 10%. Balanced against what are primarily aesthetic reasons for using talc in genital hygiene, the risk benefit decision is not complex. Appropriate warnings should be provided to women about the potential risks of regular use of talc in the genital area.

REFERENCES

BOOTH, M., BERAL, V. and SMITH, P., Risk factors for ovarian cancer: a case-control study. *Brit. J. Cancer,* **60**, 592–598 (1989).

CHANG, S. and RISCH, H., Perineal talc exposure and risk of ovarian carcinoma. *Cancer*, **79,** 2396–2401 (1997).

CHEN, Y., WU, P.C., LANG, J.H., GE, W.Y., HARTGE, P. and BRINTON, L.A., Risk factors for epithelial ovarian cancer in Bejing, China. *Int. J. Epidemiol.,* **21,** 23–29 (1992).

COOK, L.S., KAMB, M.L. and WEISS, N.S., Perineal powder exposure and the risk of ovarian cancer. *Amer. J. Epidemiol.,* **145,** 459–465 (1997).

CRAMER, D.W., WELCH, W.R., SCULLY, R.E. and WOJCIECHOWSKI, C.A., Ovarian cancer and talc. *Cancer,* **50,** 372–376 (1982).

GREEN, A., PURDIE, D., BAIN, C., SISKIND, V., RUSSELL, P., QUINN, M., WARD, B. and SURVEY OF WOMEN'S HEALTH STUDY GROUP, Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. *Int. J. Cancer,* **71,** 948–951 (1997).

HARLOW, B.L., CRAMER, D.W., BELL, D.A. and WELCH, W.R., Perineal exposure to talc and ovarian cancer risk. *Obstet. Gynecol.,* **80,** 19–26 (1992).

HARLOW, B.L. and WEISS, N.S., A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. *Amer. J. Epidemiol.,* **130,** 390–394 (1989).

HARTGE, P., HOOVER, R., LESHER, L.P. and MCGOWAN, L., Talc and ovarian cancer (letter). *J. Amer. Med. Ass.,* **250,** 1844 (1983).

HELLER, D.S., WESTHOFF, C., GORDON, R.E. and KATZ, N., The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Amer. J. Obstet. Gynecol.,* **174,** 1507–1510 (1996).

HENDERSON, W., HAMILTON, T. and GRIFFITH, K., Talc in normal and malignant ovarian tissue. *Lancet,* **5**, 449 (1979).

HERR, J.C., HEIDGER, P.M., SCOTT, J.R., ANDERSON, J.W., CURET, L.B. and MOSSMAN, H.W., Decidual cells in the human ovary at term I. Incidence, gross anatomy and ultrastructural features of merocrine secretion. *Amer. J. Anat.,* **152,** 7–28 (1978).

KEAL, E.E., Asbestosis and abdominal neoplasms. *Lancet,* **2**: 1211–1216 (1960).

KLEINFELD, MESSITE, J., KOOYMAN, O. and ZAKI, M.H., Mortality among talc miners and millers in New York State. *Arch Environ. Health,* **14,** 663–667 (1967).

PURDIE, D., GREEN, A., BAIN, C., SISKIND, V., WARD, B., HACKER, N., QUINN, M., WRIGHT, G., RUSSELL, P. and SUSIL, B., Reproductive and other factors and risk of epithelial ovarian cancer; an Australian case-control study. *Int. J. Cancer,* **6,** 678–684 (1995).

ROSENBLATT, K.A., SZKLO, M. and ROSENSHEIN, N.B., Mineral fiber exposure and the development of ovarian cancer. *Gynecol. Oncol.,* **45,** 20–25 (1992).

SHUSHAN, A., PALTIEL, O., ISCOVICH, J., ELCHALKAL, U., PERETZ, T. and SCHENKER, J.G., Human menopausal gonadotropin and the risk of epithelial ovarian cancer. *Fertil. Steril.,* **65,** 13–18 (1996).

TZONOU, A., POLYCHRONOPOULOU, A., HSIEH, C.C., REBELAKOS, A., KARAKATSANI, A. and TRICHOPOULOS, D., Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int. J. Cancer,* **55,** 508–510 (1993).

VENTER, P.F. and ITURRALDE, M., Migration of particulate radioactive tracer from the vagina to the peritoneal cavity and ovaries. *S. Afr. med J.,* **55,** 917–209 (1979).

WHITTEMORE, A.S., WU, M.L., PAFFENBARGER, R.S., SARLES, D.L., KAMBERT, J.B., GROSSER, S., JUNG, D.L., BALLEN, S. and HENDRICKSON, M., Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder tobacco, alcohol, and coffee. *Amer. J. Epidemiol.,* **128,** 1228–40 (1988).

YOUNG, R.H., CLEMENT, P.B. and SCULLY, R.E., The Ovary (chapter 53). *In* Sternberg, S.S. (ed.), *Diagnostic Surgical Pathology* (2nd Ed.), p. 2213, Raven Press, New York (1994).

Exhibit 55

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TALC AND CARCINOMA OF THE OVARY AND CERVIX

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Summary

An extraction-replication technique was used to examine tissue from patients with ovarian and cervical tumours. In both conditions talc particles were found deeply embedded within the tumour tissue. The close association of talc to the asbestos group of minerals is of interest.

THE development in this laboratory of an extraction-replication technique (Henderson, 1969) for the study of foreign particles within tissues has allowed the *in situ* identification of crocidolite asbestos within the tissue of various mesotheliomas (Henderson *et al.*, 1969) removed from patients who had been concerned with the manipulation of asbestos in industry. This technique has now been applied to the study of tissue from ovarian and cervical carcinoma.

MATERIALS AND METHODS

Tissue

The tissue studied was obtained from patients with cancer of either the ovary or the cervix, and was first prepared as paraffin sections for normal routine histological examination but was unstained. Sections were then stained for histological assessment in the usual manner, and adjacent unstained tissue prepared for electron microscopy.

Replication Technique

The extraction-replication procedure has been described (Henderson, 1969). Sections of tissue were immersed in xylene and in ethanol, and the dehydrated tissue was then embedded by impressing the section on to the surface of a thin sheet of acetone-softened cellulose acetate, mounted on a glass slide, and left to harden. On removing the slide, the embedded tissue was left in the cellulose acetate. The tissue was then outlined with thin strips of Scotch tape to form a shallow well, and a 10 per cent (v/v) polyvinyl alcohol (PVA) solution applied. When the PVA had hardened it was stripped from the section providing a replica of the tissue surface. Foreign particles associated with the tissue are often removed with the PVA during this stripping process.

A complete sequential examination through the embedded tissue is possible by taking successive strippings. These surface replicas were then preshadowed with platinum, a carbon film deposited for strength, and the PVA removed by floating the replica in a hot water bath. Replicas were mounted on electron microscope grids for examination, using the AEI-6B microscope.

RESULTS

No asbestos particles were found in any of the tissue studied. Particles of talc were identified in approximately 75 per cent (10 of 13) of the

FIG. 1

Typical decoration pattern on a particle of natural talc. Numerous crystal lattice planes are shown (a). (×30 000.) Scale refers to 1·0 μ.

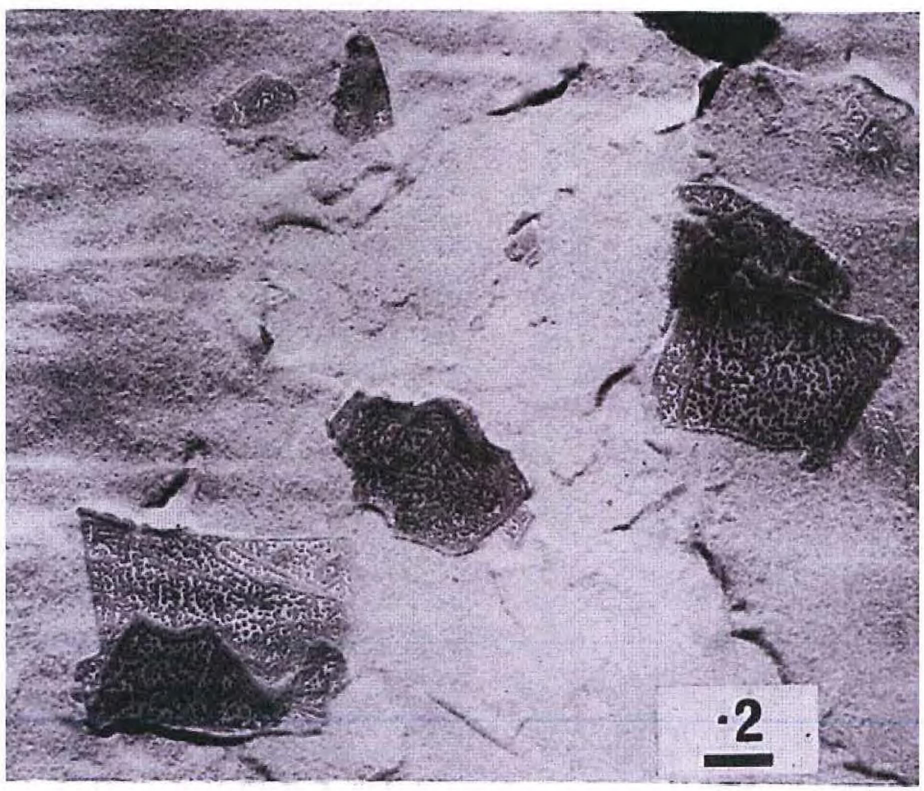

FIG. 2

Commercial talc preparations illustrating the decoration pattern. (×40 000.)

FIG. 3

Micrograph of tissue from a serous papillary cystadeno-carcinoma of the ovary removed from a 27-year-old female. No previous abdominal operations had been carried out. The decoration pattern and lattice planes are shown. ($\times$ 30 000.)

ovarian tumours. Using the replication technique identification of talc is possible because of the characteristic "decoration pattern" induced by the evaporation of platinum *in vacuo* on the crystal surface. Figure 1 shows this pattern on a particle of *natural* talc and the distinctive lattice planes of the crystals. Anthophyllite asbestos, which is known to be converted naturally to talc, is the only crystalline material which is at present indistinguishable from talc by using the replication technique. The decoration pattern on material from a commercial talc preparation is also demonstrated in Figure 2.

Material found within the ovarian tumours and identified as talc is illustrated in Figure 3. The talc particles were found deep within the tumour tissue. Some were as small as 1000Å in size but they were generally within a range from 1000Å to 2 μ.

Talc particles were also found embedded within tumours of the cervix. Figure 4 shows one such particle embedded in a capillary wall within the tumour, and Figure 5 illustrates the decoration pattern of the particle at a higher magnification. Crystals as large as 5 μ. were found in tissue from the cervical tumours and were generally larger than those seen in the ovarian tumours. Talc crystals were found in

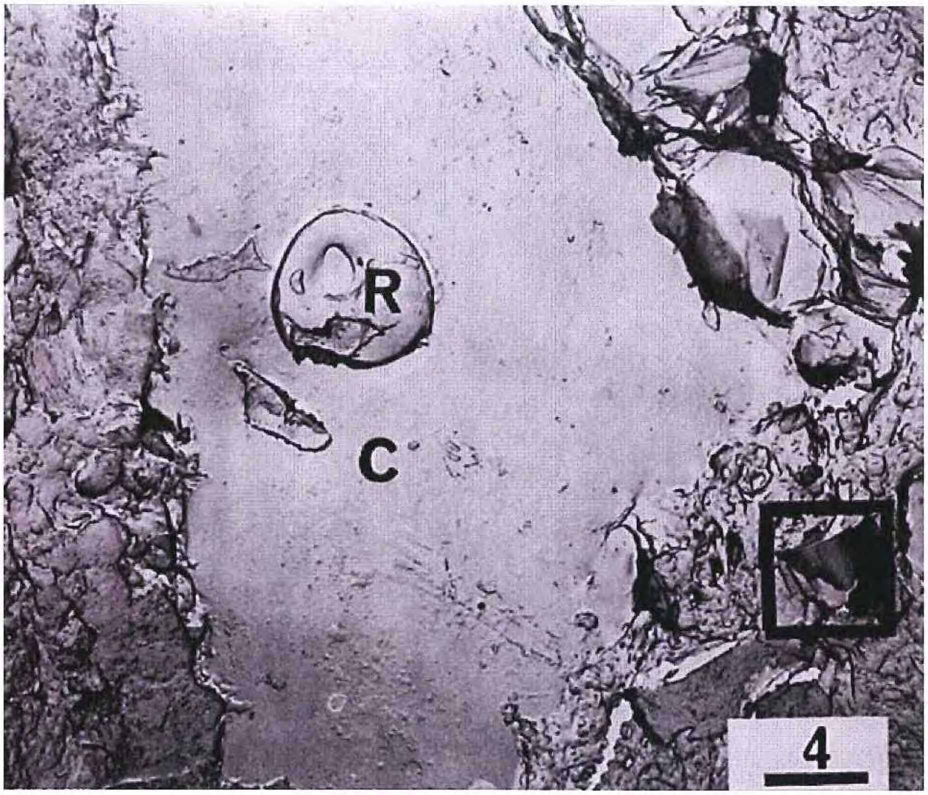

FIG. 4

Micrograph of tissue from a squamous-cell carcinoma of the cervix from a 62-year-old female. C—capillary, R—red cell. The particle of talc can be seen in the wall of the capillary. (×3500.)

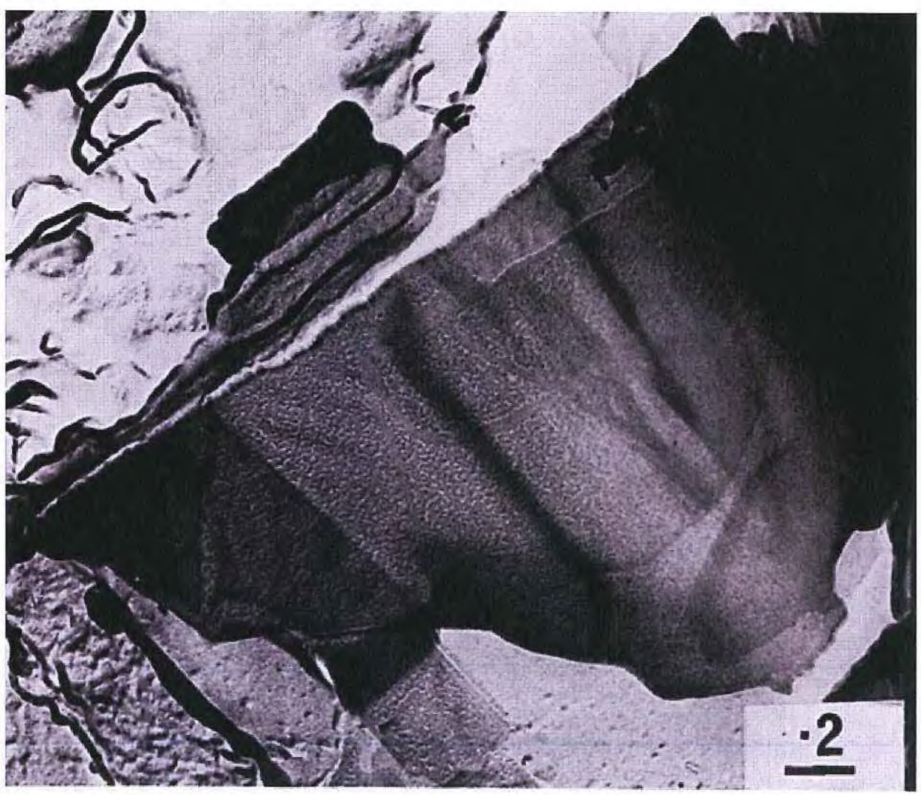

FIG. 5

A higher magnification of the talc particles outlined in Fig. 4. The typical decoration pattern is shown. (×40 000.)

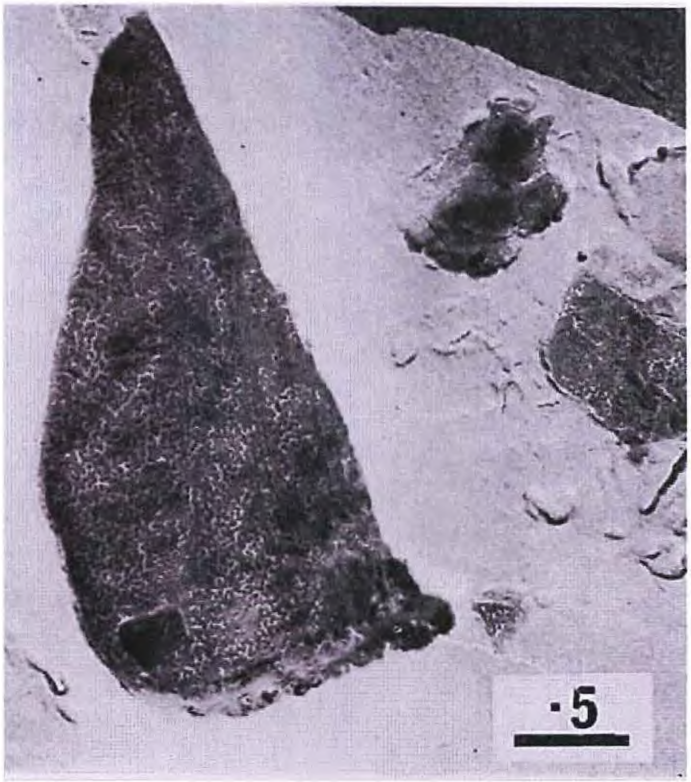

FIG. 6
Talc particles found in tissue from a pneumoconiotic lung. (×30 000.)

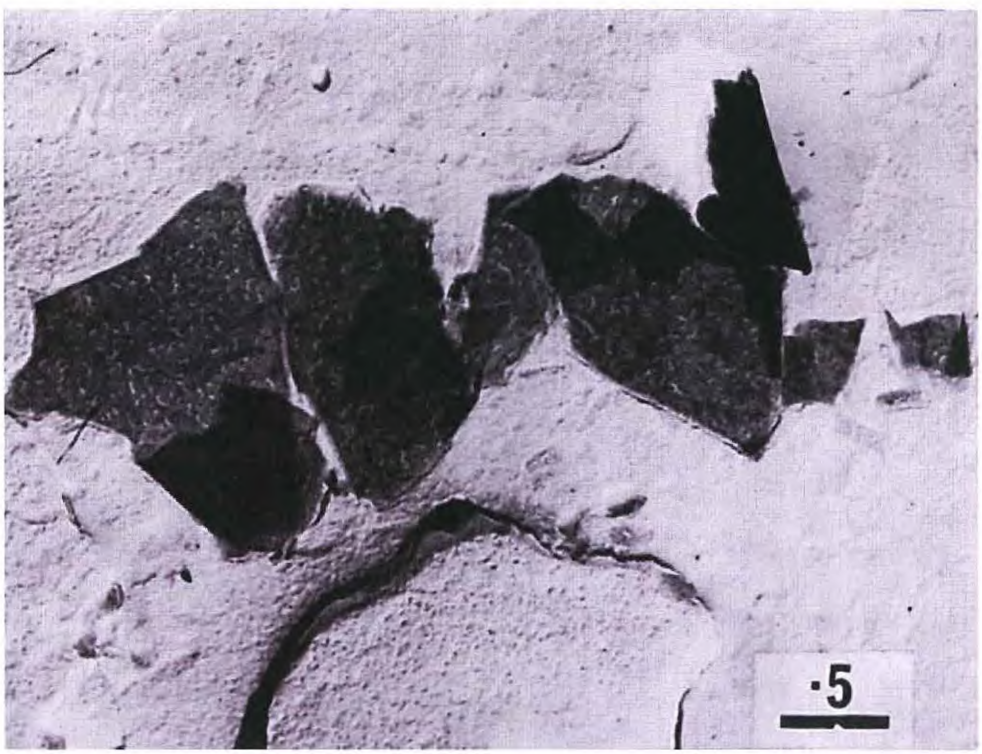

FIG. 7
Micrograph from the deepest part of an extensive papillary adenocarcinoma entirely replacing the endometrium in a 58-year-old woman, 8 years postmenopausal. Both ovaries were enlarged by hilar metastases, showing histological features similar to the primary endometrial lesion. Numerous talc particles were found in the primary endometrial carcinoma, but none in the metastatic ovarian tumours. (×26 000.)

approximately 50 per cent of the cervical tumours examined (12 of 21) but it must be realized that these particles are extremely minute, often with the dimensions of viruses, and only small regions of the tumour tissue could be studied. Approximately ten replication "strippings" for electron-microscope examination are usually taken from each thin section of the tissue. Figure 6 illustrates the use of the technique in the examination of pneumoconiotic lung tissue from a patient whose industrial history indicated long exposure to Norwegian talc.

Many particles of talc were found concentrated in the deeper layers of a primary carcinoma of the endometrium (Fig. 7) whereas extensive studies of a secondary tumour in the ovary in the same patient did not show the presence of talc. Application of the technique to "normal" ovarian tissue removed from patients with breast cancer has also shown talc particles in 5 of 12 such tissues studied. Extensive study at high magnification with the electron microscope is, however, required for evaluation of a replica and particles could easily be missed.

The application of electron-microscope microanalysis (EMMA-AEI, Harlow, England) to the particles extracted by the replication technique has provided preliminary evidence that the crystals contain magnesium and silicon, talc being a magnesium silicate.

Discussion

The possibility that the increasing incidence of carcinoma in western society may be related to a corresponding increase in the use of asbestos (Graham and Graham, 1967) is of interest, especially with regard to pleural and peritoneal mesotheliomas in workers exposed to crocidolite asbestos in industry (Wagner *et al.*, 1960; Elwood and Cochrane, 1964). There have been a number of reports about the relationship between asbestos and carcinogenesis (Smith *et al.*, 1965; Jacob and Anspach, 1965). However, the identification of asbestos fibres within tissue is extremely difficult. Fine particles embedded within tumour tissue are usually beyond the limits of resolution of the optical microscope, and tissue incineration, followed by electron microscopy of the isolated particles, may be unreliable if chemical changes are induced by the procedure. Using normal light microscopy, identification of asbestos particles is based on the presence of characteristic ferritin bodies on some of the fibres, although these cannot easily be distinguished from similar bodies around elastin fibres (Henderson *et al.*, 1970). This procedure may not, however, be as unreliable as the use of polarized light for the demonstration of brightly illuminated "birefringent crystals of asbestos".

The replication technique (Henderson, 1969) failed to show asbestos fibres in the ovarian neoplasms studied. On the other hand, there was good evidence for the presence of talc, often indistinguishable from anthophyllite asbestos, within the ovarian tissue. (Anthophyllite is converted naturally to talc.) The talc particles were found localized deep within tumour tissues, and not universally dispersed throughout the tumour. The talc particles in the ovary were generally much smaller than those found in the tissue from the tumours of the cervix.

The relationship between asbestos and mesotheliomas appears well established, and the replication technique has provided unequivocal evidence for the presence of fibres within such tumours. This technique has also produced evidence for the presence of talc in tissue from pneumoconiotic lungs of a patient with an industrial history of exposure to Norwegian talc (Henderson *et al.*, 1970). The presence of mica, kaolin and asbestos fibres were also identified in tissue from these pneumoconiotic lung tissue.

Although it is impossible to incriminate talc as a primary cause of carcinomatous changes within either the cervix or the ovary on the preliminary observations described here, the possibility that talc may be related to other predisposing factors should not be disregarded and further investigations are obviously required.

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References

Elwood, P. C., and Cochrane, A. L. (1964): *British Journal of Industrial Medicine*, **21**, 304.

Graham, J., and Graham, R. (1967): *Environmental Research*, **1**, 115.

Henderson, W. J. (1969): *Journal of Microscopy*, **89**, 369.

Henderson, W. J., Gough, J., and Harse, J. (1970): *Journal of Clinical Pathology*, **23**, 104.

Henderson, W. J., Harse, J., and Griffiths, K. (1969): *European Journal of Cancer*, **5**, 621.

Jacob, G., and Anspach, M. (1965): *Annals of New York Academy of Sciences*, **132**, 536.

Keal, E. E. (1960): *Lancet*, **2**, 1211.

Smith, W. E., Miller, L., Elsasser, R. E., and Hubert, D. D. (1965): *Annals of New York Academy of Sciences*, **132**, 456.

Wagner, J. C., Sleggs, C. A., and Marchand, P. (1960): *British Journal of Industrial Medicine*, **12**, 260.

Exhibit 56

The relationship between perineal cosmetic talc usage and ovarian talc particle burden

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OBJECTIVE: Epidemiologic studies support the hypothesis of a dose-related risk of epithelial ovarian cancer with perineal talc exposure. Frequency and duration of talc usage has not been previously correlated with ovarian talc content.

STUDY DESIGN: Ovaries were studied from 24 women undergoing incidental oophorectomy who were interviewed regarding talc usage. Twelve subjects reported frequent perineal talc applications; the twelve controls reported no use. Ovarian tissue blocks were digested and analyzed by polarized light microscopy and analytic electron microscopy to identify and quantify talc.

RESULTS: Talc was identified in all 24 cases by either light or electron microscopy. Talc particle counts were completely unrelated to reported levels of perineal talc exposure.

CONCLUSIONS: The detection of talc in all ovaries demonstrates that it can reach the upper genital tract. Widespread exposure to talc during diapering may contribute to the ubiquitous presence of talc in ovarian tissue. (AM J OBSTET GYNECOL 1996;174:1507-10.)

Key words: Talc, ovary

Epidemiologic evidence suggests that perineal exposure to talc is associated with an increased risk of epithelial ovarian cancer in a dose-related fashion.[1-5] Other epidemiologic studies have shown no increased risk of ovarian cancer associated with talc.[6,7] Studies show access of particulate matter into the female peritoneal cavity through the transvaginal route.[8-10] A few reports have identified talc in ovarian tissue,[11,12] both benign and malignant, but these data were not correlated with an exposure history. Other potential genital tract exposures in a woman's life include surgical gloves,[13] condoms, and diaphragms. Diapering with talc during infancy is another potential exposure. Epidemiologic studies have not linked these exposures to an increased risk of ovarian cancer.[1,2]

If transvaginal transport of perineally applied talc occurs, women with the heaviest exposures may show the largest talc particle burdens in their ovaries. Tissue digestion techniques are an accepted analytic adjunct in the identification and quantification of asbestos in the lungs of occupationally exposed individuals[14,15] and are useful in the identification and quantification of talc as well. The goal of this pathoepidemiologic study was to correlate the history of perineal talc usage with the talc particle burden found in the ovaries.

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0002-9378/96 $5.00 + 0 ***6/1/70003***

Material and methods

In a case control study of benign ovarian neoplasms at Columbia Presbyterian Medical Center, women undergoing surgery from 1992 to 1993 were interviewed regarding various factors, including talc usage. Subjects were also questioned regarding possible occupational exposures to asbestos, and mothers were contacted regarding diapering history whenever feasible.

Subjects were categorized for talc exposures as follows. Women who reported no direct application of talc to the perineum or to underwear were considered unexposed. For women who reported talc application to underwear or the perineum, the total number of lifetime applications was estimated as the average frequency of use times the number of years of use. For instance, a woman who reported perineal talc application twice per day for 10 years was considered to have 7240 applications. To simplify the classification of exposed and unexposed women, subjects who reported tubal ligation, diaphragm use, or feminine hygiene spray use were excluded from this analysis.

Interviewed subjects from the parent case control study who had a normal contralateral ovary in the surgical specimen were eligible for this substudy. Sections of normal ovary from the 12 women who reported the largest number of perineal talc applications were analyzed. For each of these subjects the unexposed woman closest in age was selected as a control. In addition, the ovaries of two stillborn fetuses were analyzed as negative controls.

Table I. Talc particle counts in women who reported perineal cosmetic talc usage

Subject No.	*age (yr)*	*Lifetime talc applications**	*EM talc particle counts†*	*Polarized light microscopic counts†*	*Asbestos detected*	*Talc use with diapering*
1	49	4,784	1,600,288	96	No	Yes
2	49	5,475	0	54	No	Unknown
3	57	6,552	0	100	Yes	No
4	31	8,144	0	114	No	Unknown
5	43	10,556	0	464	Yes	Unknown
6	45	11,284	151,300	300	No	Yes
7	50	11,648	236,406	345	No	Yes
8	57	15,600	0	75	No	Yes
9	66	18,980	0	250	Yes	Yes
10	47	21,840	1,576,000	111	No	Unknown
11	44	23,660	0	348	No	Yes
12	44	39,312	7,565,000	26	Yes	Unknown

EM, Electron microscopy.
*Frequency of use × Years of use.
†Per gram wet tissue weight.

Ovarian tissue in blocks was deparaffinized, rehydrated, blotted dry, and weighed. Digestion with 5% potassium hydroxide was performed at 70° C for 2 to 4 hours. After complete digestion, the tissue was centrifuged at 12,000 revolutions/min for 20 minutes. The potassium hydroxide was removed, leaving a pellet to which approximately 20 ml of distilled water was added. The pellet was resuspended by use of a microultrasonic cell disrupter at 50 W for 5 seconds. Centrifugation, distilled water wash, and microultrasonic cell disrupter were repeated three times. The distilled water was removed, and the pellet was resuspended in 5 to 10 ml of distilled water. Drops of 10 µl of the final suspension were placed on nickel formvar and carbon-coated locator grids and air-dried. Transmission electron microscopy to identify particles and their size was performed. The identity of the particles was determined by energy-dispersive spectroscopy and confirmed by electron diffraction. Grids were viewed at both 10,000 and 19,000 diameters. All talc particles observed were counted. Cytospin slides for polarized light microscopy were prepared from the same final suspension as the electron microscopy grids. Polarized light microscopy counted larger talc particles (limits of detection approximately 1 µm), whereas electron microscopy detected smaller ones (limits of detection approximately 0.5 nm).

Routinely, all solutions are checked for detectable limits of contaminating particles; all places where particles could have contaminated the specimen, such as paraffin, are also controlled for.

Associations between talc exposure and talc particle count in the 12 exposed subjects were assessed with Spearman's rank correlation coefficient.

Results

Detailed results can be seen in Tables I and II. The mean age of the patients was 49 years (range 29 to 66 years). For eight exposed subjects, a control was found who was within 4 years of her age. Talc particle counts were not related to age in either the exposed or unexposed subjects ($p > 0.25$). The mean number of lifetime exposures for the women reporting perineal talc use was 14,820 (range 4784 to 39,312). Talc was detected in all ovaries by either polarized light or electron microscopy. There was a wide range of values, as shown by the large SDs. Table III shows that talc particles were observed to a similar extent with both exposed and unexposed subjects.

Neither the light microscopic nor electron microscopic values correlated with reported perineal talc usage (p values 0.37 and 0.45). There was a negative correlation between the values obtained by light microscopy and electron microscopy ($r = -0.34$, $p = 0.05$). An attempt to contact mothers of subjects was successful for 11 of the 24 subjects. Ten of these reported using talc to diaper their babies, which indicates that lifetime talc exposure may be underestimated for nearly all the subjects. Analyses of two fetal ovaries and a pair of surgical gloves was completely negative for talc.

In one subject we studied both ovaries; on the right side we detected no talc by electron microscopy and 556 particles by light microscopy, and on the left side we detected 1,669,000 particles per gram of wet weight by electron microscopy and 6 particles by light microscopy. Hematoxylin-eosin stained slides from the analyzed sections of tissue were examined. There was no evidence of response to talc, such as foreign body giant cell reactions or fibrosis in the tissue. Asbestos was detected in ovaries of five of the subjects with no talc exposure and in four ovaries of the talc-exposed subjects.

Comment

If transvaginal transport of perineally applied talc occurs, we would expect women with the heaviest exposures to show the largest talc particle burden in their ovaries.

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Table II. Talc particle counts in women without history of perineal cosmetic talc usage

Subject No.	*Age (yr)*	*Reported exposure history*	*EM talc particle count**	*Polarized light microscopic talc particle counts**	*Asbestos detected*	*Talc use with diapering*
1	63	0	1,350,000	89	No	Yes
2	57	0	315,250	111	No	Yes
3	29	0	0	42	No	Unknown
4	48	0	1,669,000	6	Yes	Unknown
5	59	0	315,208	166	Yes	Yes
6	40	0	0	69	Yes	Yes
7	43	0	0	566	Yes	Unknown
8	64	0	0	420	Yes	Yes
9	49	0	0	53	No	Unknown
10	54	0	0	1139	No	Unknown
11	32	0	63,042	2200	No	Unknown
12	58	0	472,813	0	No	Unknown

EM, Electron microscopy.
*Per gram wet tissue weight.

Table III. Comparison of particle burdens between reported exposed and nonexposed subjects

Talc exposure	*No. of subjects with talc by EM*	*No. of subjects with talc by light microscopy*	*Mean EM particle count**	*SD*	*Mean light microscopic particle count**	*SD*
Reported talc use ($n = 12$)	5/12	12/12	927,416	2,174,888	190	144
No reported talc use ($n = 12$)	6/12	11/12	348,776	570,055	405	655

EM, Electron microscopy.
*Per gram wet tissue weight.

Tissue digestion techniques have been used to identify and quantify particle burdens of various organic materials in human tissue. The most notable use of this technique is in the identification of asbestos in the lungs of occupationally exposed individuals.[14, 15] Other studies have examined other organs as well. In the 1979 report of Henderson et al.[11] ovaries were studied after an oxygen incineration procedure. They found 6900 to 55,100 talc particles per gram of wet weight in three normal ovaries, 17,400 to 24,300 in three cystic ovaries, and 6400 to 24,500 in three ovarian adenocarcinomas. No exposure histories were stated.

Our study attempted to correlate ovarian talc particle burden with exposure history. Our results do not support a linear dose-related ovarian talc particle burden. However, the mean electron microscopic particle count was much higher in talc users. Perhaps perineal talc does contribute to the ovarian particle burden; however, factors other than dosage may contribute. Other factors to consider include method of application, type of talc, and the possible contribution of inhaled talc particles. The range of talc particle values obtained in this study was wide, as evidenced by the large SDs. This spread of values was also present in the study of Henderson et al.[11] and in much of the asbestos fiber burden literature. Talc may be unevenly distributed throughout the ovarian parenchyma. This is supported by the discrepant counts we obtained on the one subject who had analysis of both ovaries. The lack of correspondence between polarized light and electron microscopy counts was due to measurement of different size particles.

Undocumented exposures to talc may partly explain the lack of correlation between adult histories of perineal cosmetic talc applications and ovarian burdens. Although both examination and surgical gloves in the past were dusted with talc, we cannot document this exposure. The gloves we currently use are talc free, according to the company and to our analyses. Ten of the 11 available mothers reported using talc while diapering their babies; this ubiquitous exposure may also contribute to the ovarian particle burdens.

Talc as a possible etiologic agent in the development of epithelial ovarian cancer may be related to asbestos exposure in several ways. Aside from the chemical similarities between the two, many cosmetic talcs contained significant amounts of asbestos, particularly before 1976.[1] Although tremolite asbestos has been documented as a containment of some talc preparations, the types of asbestos detected here are more commonly associated with an environmental (chrysotile) or occupational (chrysotile and crocidolite) exposure.[16]

The detection of talc in all the ovaries demonstrates

that talc can reach the upper genital tract. However, the quantity detected in this study did not correlate well with the reported exposure. Further study is required to elucidate whether the presence of talc in ovarian tissue is pathogenic.

REFERENCES

1. Cramer D, Welch W, Scully RE. Ovarian cancer and talc: a case control study. Cancer 1982;50:372-6.
2. Harlow B, Cramer D, Bell D, Welch W. Perineal exposure to talc and ovarian cancer risk. Obstet Gynecol 1992;80:19-26.
3. Harlow B, Weiss N. A case-control study of borderline ovarian tumors: the influence of perineal exposure to talc. Am J Epidemiol 1989;130:390-4.
4. Longo D, Young R. Cosmetic talc and ovarian cancer. Lancet 1979;2:349-51.
5. Scully RE. Ovarian tumors—a review. Am J Pathol 1977;87: 686-720.
6. Hartge P, Stewart P. Occupation and ovarian cancer: a case-control study in the Washington DC metropolitan area 1978-81. J Occup Med 1994;36:924-7.
7. Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. Int J Cancer 1993;55:408-10.
8. Egli G, Newton M. The transport of carbon particles in the human female reproductive tract. Fertil Steril 1961;2:151-5.
9. Henderson W, Hamilton T, Baylis M, Pierrepoint CG, Griffiths K. The demonstration of the migration of talc from the vagina and posterior uterus to the ovary in the rat. Environ Res 1986;40:247-50.
10. Scully RE. Atlas of tumor pathology, second series, fascicle 16: tumors of the ovary and maldeveloped gonads. Washington, DC: Armed Forces Institute of Pathology, 1979.
11. Henderson W, Hamilton T, Griffith K. Talc in normal and malignant ovarian tissue. Lancet 1979;5:499.
12. Henderson W, Joslin C, Turnbull A, Griffiths K. Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw 1971;78:266-72.
13. Henderson W, Melville-Jones C, Barr W, Griffiths K. Identification of talc on surgeons' gloves and in tissue for starch granulomas. Br J Surg 1975;62:941-4.
14. Heller D, Gordon R. Demonstration of asbestos fibers in a ten year old sputum sample. Am J Ind Med 1991;20:415-9.
15. Roggli V, Pratt P. Number of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. Hum Pathol 1983;14:355-61.
16. Heller D, Gordon RE, Westhoff C, Gerber S. Asbestos exposure and ovarian fiber burden. Am J Ind Med (in press).

Exhibit 57

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE JOHNSON & JOHNSON (LHG) TALCUM POWDER PRODUCTS MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION ***THIS DOCUMENT RELATES TO ALL CASES***	**MDL NO. 16-2738 (FLW)**

RULE 26 EXPERT REPORT OF
SARAH E. KANE, MD

Date: November 15, 2018

Sarah E. Kane, MD

I. BACKGROUND:

I am certified by the American Board of Pathology in Anatomic Pathology, Clinical Pathology and Cytopathology. I received my medical degree from The Ohio State University College of Medicine in Columbus, Ohio. I completed my residency in Anatomic and Clinical Pathology at Massachusetts General Hospital, a Harvard Medical School teaching hospital in Boston, Massachusetts. Following my residency, I completed a two-year gynecologic and cytology fellowship as the Robert E. Scully Fellow in Pathology at Massachusetts General Hospital, named after Dr. Robert Scully, who was a giant in the field of gynecologic pathology. This fellowship was focused on gynecologic pathology, perinatal pathology, and cytopathology. I studied the causes and mechanisms of disease as part of my training, and studied gynecologic cancer and disease in depth during my fellowship training. To this day, I routinely follow the gynecologic pathology literature as part of my regular practice.

I am currently a full partner in a private practice group, Commonwealth Pathology Partners PC. I have staff privileges at Massachusetts General Hospital, North Shore Medical Center (consisting of Salem Hospital in Salem, MA and Union Hospital in Lynn, MA) and Newton-Wellesley Hospital. I was hired by Commonwealth Pathology Partners PC to be the group's gynecologic pathology expert. Although all of the anatomic pathologists in our group practice general anatomic pathology, our group employs fellowship-trained pathologists in many subspecialty areas of pathology. This means that I see the majority of gynecologic surgical pathology specimens from my hospital sites, and if another pathologist needs an opinion on a gynecologic case, I will review it. I also presently serve as the autopsy director at North Shore Medical Center. I regularly attend and participate in numerous multidisciplinary conferences at Massachusetts General Hospital at the Cancer Center site in Danvers, MA.

Before entering private practice, I was a staff pathologist and Instructor of Pathology at Beth Israel Deaconess Medical Center (BIDMC), another Harvard Medical School teaching hospital. During my time at BIDMC, I performed specialty sign-out in gynecologic pathology, perinatal pathology and cytology. I was also served as the Associate Director of the Cytopathology Fellowship Program at BIDMC, served on numerous pathology department committees, and taught several courses at Harvard Medical School before I was recruited for my current position. My curriculum vitae is attached as Exhibit A. It further details these positions and the remainder of my work experience in this field. Exhibit B details the references cited in this report, as well as other materials and data I considered.

I have been asked to provide an expert report regarding my opinions on the question of general causality in the case of talcum powder product use and ovarian cancer. All of my opinions stated below are held to a reasonable degree of medical and scientific certainty. I reserve the right to modify or change my opinion based on further documents or information that may be provided to me in the future.

A pathologist is a physician who has completed medical school and a post-graduate residency in pathology (either clinical pathology, anatomic pathology, or both).Like me, many pathologists go on to complete fellowships following their education and residency.

Pathology is the study of disease; pathologists spend much of their time both in training and in daily practice studying the causes and presentations of disease. The years of medical training are of critical importance in daily practice; pathologists must make clinical assessments, based in part on medical and epidemiologic knowledge, about identification of causes, risk factors, clinical sequelae, morphologic, and genetic features of disease.

In order to produce accurate diagnoses, pathologists must be knowledgeable about the medical, scientific, and epidemiologic evidence base. A knowledge of advancements in technologies applied to tissue samples must be continuously maintained. This involves not only maintaining current knowledge of the pathology literature, but also of the literature in various other fields such as oncology and other fields relevant to our practice.

One of the tools used in the process of identifying talc particles in tissue is polarized light microscopy. Anatomic pathologists routinely use polarized light microscopy in clinical practice. As an example, one might use polarized light microscopy to find foreign material and explain an inflammatory reaction. The most common application in my practice is for identifying calcium oxalate crystals in breast biopsies done for radiologically identified calcifications. I estimate I use polarized light microscopy for this purpose about twice a month.

In anatomic pathology, the pathologist not only needs to be aware of the numerous possible diagnoses, but also of the causes of diseases one may encounter in any given organ system. Coming to a diagnosis requires knowledge of the medical, scientific, and epidemiologic literature. Pathologists must be proficient in the current literature that informs and supports their conclusions.

Ultimately, a pathologist's diagnosis must make biological sense and must be supported by the weight of the available medical and scientific information. Not only must a particular case match the morphological characteristics of the diagnosis being made, but it must fit the clinical presentation, the patient history, and it must be consistent with what is known about the disease, including what is known about disease causation. These are the same medical and scientific information resources that I rely on for my opinions in this report.

Thus, the work that I've done in this report is similar to what I do in my daily practice. My clinical practice requires ongoing familiarity with the same medical evidence that I have considered here.

Ovarian cancer has an incidence rate of 11.8 per 100,000, and thus is relatively rare (Torre 2018). At my current private practice, I am the primary pathologist on approximately 6,000 cases annually. This includes both surgical pathology and cytopathology cases. I would be diagnosing, ruling out, or looking for ovarian cancer or metastatic ovarian cancer (among other diseases), in approximately 2000 cases a year as a rough estimate. Of those, I estimate that I diagnose about 30 cases per year as ovarian tumors. Academic teaching hospitals generally tend to have a higher volume of ovarian tumor cases due to their large referral bases. While I was a staff pathologist at Beth Israel Deaconess Medical Center, the pathology department implemented a subspecialty sign-out schedule in 2010. In my last two years there,

I signed out predominantly gynecologic surgical pathology in addition to cytopathology (in prior years the department had a general surgical pathology schedule, which meant all types of cases went to each anatomic pathologist regardless of subspecialty fellowship training). During that time, I estimate I signed out about 500 ovarian tumor cases per year. Similarly, while I was a fellow at Massachusetts General Hospital from 2005-2007, I independently signed out gynecologic surgical pathology and estimate I signed out approximately 500 ovarian tumor cases per year. As a resident in anatomic pathology at Massachusetts General Hospital, I was exposed to hundreds of ovarian tumor cases both during my clinical case work and didactic sessions.

Of note, during my time at Massachusetts General Hospital, both Drs. Robert Scully and Debra Bell were still working in the Department of Pathology. Dr. Scully was a co-author on Dr. Cramer's first paper on talc and ovarian cancer in 1982, and Dr. Bell was a co-author on Drs. Harlow and Cramer's 1992 paper on talc and ovarian cancer. Dr. Bell's tenure as Cytopathology Director also overlapped with my time there. This meant that I spent significant time with Dr. Bell during my residency and fellowship. I was the primary author of a paper on ovarian serous borderline tumors in 2006, with Dr. Bell serving as a co-author. Dr. Scully, known as a giant in gynecologic pathology, was semi-retired by the time I started my pathology residency in 2001. However, he was at the hospital nearly every day and all of the gynecologic pathologists would still show him cases on a consult basis. Dr. Robert Young, the director of my fellowship program, was a Scully protege and continued his consulting practice. It is because of my training at Massachusetts General Hospital and my interactions with both Drs. Scully and Bell that I first became aware of their work on talc and ovarian cancer. Since then, I have maintained a professional interest in and have continued to monitor developments in the science regarding talcum powder exposure and ovarian cancer, and it has been the subject of professional discussions pre-dating this litigation.

My billing rate is $500 per hour. I have previously testified in one matter, a deposition for the case of Julie Lagadimas, as Personal Rep. of the Estate of Dawn M. O'Toole v. R.J. Reynolds Tobacco Co., et al; Norfolk Super. Ct. Case No. 1582-CV-01474.

II. GENERAL CAUSATION OPINIONS:

Based on assessing and weighing the totality of the evidence, and following the methodology set forth below, I hold the following opinions to a reasonable degree of scientific and medical certainty:

1. Talcum powder products and their constituent minerals can reach the ovaries through migration up the genital tract from the perineum to the fallopian tubes and ovaries. There is also evidence that these products can be transported through the lymphatic system (Cramer 2007). Another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

2. Once reaching the ovaries, talcum powder products can cause chronic inflammation, can increase oxidative stress, and can reduce immune response. These are biologically plausible and likely mechanisms for ovarian cancer development and progression.

3. There are chemical similarities between asbestos and talc and there are striking pathological similarities between invasive serous ovarian cancer and mesothelioma.

4. There is evidence that talcum powder products manufactured by Johnson & Johnson (Johnson's Baby Powder and Shower to Shower) have contained and continue to contain asbestos, talc containing asbestiform fibers (fibrous talc), and heavy metals such as cobalt, nickel, and chromium. Other than cobalt, which has been identified as a "possible" carcinogen by the International Agency for Research on Cancer (IARC), all of these constituents have been identified as known carcinogens by IARC (IARC 1987, IARC 2012).

5. For purposes of my opinions, I have reviewed and relied upon Dr. Crowley's report regarding the fragrance chemical constituents in Johnson & Johnson talcum powder products (Crowley Report), as well as testing reports and analysis which include, Dr. Blount (Blount Report), Dr. Longo and Dr. Mark Rigler (Longo et al. Report), as well as the corporate testimonies of John Hopkins and Julie Pier. The presence of these constituents as part of talcum powder products provides additional evidence of biological plausibility for causation regarding talc and ovarian cancer.

My opinions and conclusions are supported by epidemiologic studies showing an increased risk of ovarian cancer in women who used talcum powder products for perineal dusting, animal and in vitro studies, cellular biology studies, and pathological evidence which provides a highly biologically plausible mechanism for talc's carcinogenicity. Based on the totality of evidence, it is my opinion to a reasonable degree of scientific and medical certainty, that perineal exposure to talcum powder products can cause epithelial ovarian cancer.

III. METHODOLOGY FOR ASSESSING CAUSATION AND PRINCIPLES OF CAUSAL INFERENCE:

For this report, I followed the same methodology that I use in my clinical practice and research, a method that is generally accepted in the medical community. I used the same standards for evaluating and interpreting medical and scientific evidence, and I followed generally accepted standards in science and medicine for assessing causation, including consideration of the Bradford Hill viewpoints.

My causal assessment in this case is based on my background, training, education and experience as a physician and pathologist in interpreting, comparing, and weighing the totality of the available biologic, pathologic and epidemiologic evidence. I considered this evidence in the context of the Bradford Hill causation assessment viewpoints to reach an opinion regarding whether talcum powder products[1] can cause epithelial ovarian cancer.

Bradford Hill's discussion of a causal relationship includes strength of association, consistency, coherence, specificity, temporality, biological plausibility, dose-response, experimental evidence, and analogy as different "viewpoints" of a causal relationship between

[1] In my report, the term "talc" is used to refer to talcum powder products.

an exposure and a disease. Consideration of Bradford Hill's approach to causation, which I discuss in more detail below, supports general causation of talcum powder product exposure and ovarian cancer. The Bradford Hill causation viewpoints are not a checklist of requirements, and it does not call for a mechanical application of his 9 considerations for assessing a causal relationship; rather, it is properly understood as providing a framework for an assessment of the totality of the evidence leading to a judgment about causation. As Bradford Hill himself put it, "What I do not believe…is that we can usefully lay down some hard-and-fast rule of evidence that must be obeyed….None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as the *sine qua non*." I agree with that statement.

My methodology began with a systematic review of the medical literature to ascertain the relevant body of scientific evidence that I would consider. This included consideration of a large number of peer-reviewed publications reporting the results of human epidemiological studies investigating the association between talc exposure and ovarian cancer. I also considered and weighed other lines of evidence pertaining to explaining relevant, plausible, and likely mechanisms for how talcum powder product exposure causes ovarian cancer. This included carcinogenicity studies and data regarding talc and its constituents. Counsel for plaintiffs also provided me with medical literature to review, most of which overlapped with materials that I found independently through my own medical literature searches.

Relevance is not simply a yes/no proposition; it is a variable that ranges from not relevant to directly relevant, and there is a range between these extremes. Only a careful review of the evidence leads to an assessment of the degree of relevance. Much of science involves extrapolation and generalization from one study to the general population. The assessment of relevance is based on the extent that the study results are pertinent to the issue under consideration.

Human data is generally more relevant than animal data when assessing causation in humans. However, animal studies on exposure and disease are performed to advance our understanding of the human response to the same dose-adjusted exposure, and thus animal data is often relevant and important in that it can provide important information that forms part of the total evidence assessment. For example, if an exposure to talc in a rat causes inflammation, that could be relevant to assessing the effect in humans.

All observational studies have limitations, requiring careful interpretation. Reliability determinations focus on the degree of confidence in a study's internal validity. Reliability, like relevance, is not a yes/no proposition. For human epidemiologic observational studies, reliability assessments entail consideration of alternative explanations, including the role of chance and the likelihood that the results are affected by bias or confounding. Factors to be considered include: (1) Do we have reliable and appropriate measures of exposure; (2) do we have reliable assessments of disease; (3) do we have comparable groups for comparison; (4) have the investigators adjusted for potential confounding; (5) are the study results likely the result of a systematic bias; and, (6) does the study have enough exposures and sufficient power to detect an association if it exists?

I also consider the type of study design and whether it is suited to the question being researched. There is a general hierarchy of evidence, which I also consider, but study type and its position in the hierarchy will only have value if the study is otherwise relevant and reliable. For example, a randomized clinical trial may be the "gold standard," but one must still look at whether the study does in fact provide a relevant and reliable result for the issue of interest (here, whether talcum powder products are capable of causing ovarian cancer).

In weighing the evidence other important considerations include: How does the study define, ascertain, and measure talc exposure? What type of study was it? Other considerations include: Has the study been or can it be replicated? Is the study result consistent with other studies? Has the study been published and has it been peer reviewed? Has the study been conducted on a relevant population? How does the study adjust for potential confounders and how does the study minimize or account for bias? Is there a potential for misclassification of exposure or disease based on the circumstances under which the data was gathered or analyzed? What is the potential that study results could be due to chance, bias, or confounding? Is there a statistical analysis, with a reported error rate? Were the results statistically significant, and, if not, are the results still important when considered with all other evidence from the perspective of overall consistency? What is the size of the study population? Is the study large enough to detect an association if it exists? Do the results make biologic sense? This is a list of examples of considerations for weighing the evidence, and is not intended to be comprehensive.

In weighing the evidence, I also consider the reported "P values" and confidence intervals (the result of statistical calculations), along with the reported relative risks and odds ratios, and other details about each study as explained above and below. The concept of "statistical significance" is often misunderstood. In assessing any statistical evidence pertaining to medical issues, medical and scientific researchers note whether certain findings are "statistically significant." However, findings that are not "statistically significant" are often statistically and clinically important and should be considered and weighed along with other available evidence in making causal assessments. The concept of statistical significance using arbitrary cutoffs has no relationship to the strength or direction of an estimated association, and may have very little relationship with the actual validity of a study's results. A "P value" of 0.05 or less is often considered statistically significant, whereas 0.06 is not.[2] I agree with the epidemiologists who consider this "cut-off" to be arbitrary, because, for example, the .01 difference between p = 0.05 and p. = 0.06 is essentially the difference between a 5% vs. 6% probability that the observed association is due to the role of chance. Even where a confidence interval includes "1," depending on the values of the lower and upper bounds of the confidence interval, the most likely interpretation of the study results may be that there is an association between an exposure and the increased risk of a disease.

[2] In epidemiologic studies, epidemiologists or statisticians calculate a P-value and/or 95% confidence interval ("CI") for each risk estimate. Essentially, the P-value and the CI assess the likelihood that the observed association is due to the play of chance. A 95% CI means that if the same experiment is repeated many times, 95% of the time, the true value of the risk estimate will fall between the upper and lower bound of the CI. The narrower the CI, the more precise and reliable the risk estimate is considered to be.

Bradford Hill stated that "[n]o formal tests of significance can answer those questions [of causation]. Such tests can, and should, remind us of the effects of the play of chance… Beyond that, they contribute nothing…" Therefore, in weighing the evidence, I note the P-value and/or the confidence interval reported with a study's results, and consider this to be an important piece of information for interpreting study results. I do not think it is appropriate to disregard results just because they do not meet an arbitrary statistical threshold, a view also held by the American Statistical Association (Wasserstein 2016).

All observational studies have limitations, and the potential for "bias" and confounding. The presence of some bias is not generally a basis for scientists to disregard a study. Instead, when interpreting a study, biases must be considered and assessed for the likelihood that they may obscure, diminish, or magnify a study result, so the direction and magnitude of any bias must also be considered where possible. Some biases will have the effect of obscuring or understating an association between exposure and disease. Typically, study investigators will include as part of their published paper reporting the study results, the important strengths and limitations (including their assessment of the role of bias, chance and confounding) in the study.

In weighing the evidence, I also consider the likelihood that the study may understate or fail to detect an association that did exist (a Type II error, often due to lack of "power"); or the converse, that a study result may overstate an association or find an association that is not real (Type 1 error). In interpreting studies that do not report an association with an increased risk of ovarian cancer, one issue is whether the results provide reliable evidence of the absence of an association. The only way for data to provide statistical reassurance about the absence of an association is, in the absence of any important systematic error in the data, for the upper bound of a reasonable confidence interval (such as a 95% confidence interval) to be close to the null value.

When a study finds an association between exposure and disease, causation is one explanation, but it is not the only explanation. Other explanations must be considered and assessed. When an observational study results in a reported association between exposure and disease (i.e., relative risk or odds ratio greater than 1.0), and if alternative explanations (*i.e.*, the role of bias, confounding and chance) are considered and determined to be unlikely explanations, then causation remains a likely explanation, subject to consideration of the Hill viewpoints. In order to reach an opinion that an association is causal between talc exposure and ovarian cancer, I considered whether there are other potential explanations that better explain the relationship and which are consistent with the totality of the scientific evidence. This assessment is informed by considering how a specific study fits into the overall totality of the evidence.

My opinions on causation are informed by a review of the strengths and limitations of the epidemiology evidence along with a review of other lines of evidence, including animal data and evidence on biological plausibility, likely mechanism(s) and dose/response. Thus, as part of my methodology, I have considered whether there is an alternative explanation to causation, based on an assessment of the totality of evidence. For example, I have considered whether the findings of the human epidemiologic studies are best explained by chance,

confounding or bias, when viewed separately, and most importantly, when viewed as a whole, and in light of the several lines of experimental evidence discussed in this report.

Based on my review of the totality of evidence, which I have weighed based on the considerations described above, I conclude with a high degree of medical and scientific certainty that exposure to talcum powder products can cause ovarian cancer. Causation is the best explanation for assimilating, assessing and weighing the totality of evidence. In reaching this opinion, I found it compelling that the epidemiologic studies that captured talc exposure consistently found an association between exposure to talc applied in the perineal area and epithelial ovarian cancer. The studies also provide persuasive evidence of a dose response effect, one of the viewpoints of causality discussed by Bradford Hill. There also is persuasive evidence of plausible and likely causal mechanisms for how talc exposure leads to ovarian cancer.

The other explanations for an association (other than causation) are bias, chance and confounding, and "reverse causation."[3] While it may not possible when looking at a single study to determine whether a recall bias, or a selection bias, or a potential confounder is materially affecting the results, I find it helpful to consider how each study fits into the whole. Here, multiple studies have been conducted in different populations, by different investigators, using different methods, and using different study types, and yet there is general consistency in the results. The vast majority of studies and meta-analyses find an association with an increased risk of ovarian cancer. Under these circumstances, viewing the evidence as a whole, the likelihood that the consistent finding of an association can be explained by bias, or chance or confounding is highly unlikely, especially in light of the results of the other lines of evidence.

Finally, as part of my methodology of considering alternative explanations for the evidence, I made an effort to understand the opinions of both the plaintiff and defense experts as concerning the issue of talc and causation of ovarian cancer. In that regard I have reviewed some plaintiff and defense expert testimony and reports, which are identified on my reference list. I also cited to the extensive medical literature I considered in connection with my work on this report.

IV. MECHANISM OF TALC'S CARCINOGENICITY

There is a plausible and likely biologic mechanism whereby talc causes inflammation which can lead to epithelial ovarian cancer. Chronic inflammation has been causally linked to a number of cancers. The evidence of the relationship between inflammation and cancer is based on many studies, including studies supporting the

[3] In epidemiology, reverse causation is when the exposure-disease process is reversed; In other words, the exposure causes the risk factor. Here, the question is whether exposure to talcum powder products causes ovarian cancer or whether ovarian cancer causes increased usage of talcum powder products? I am not aware of any evidence to support a conclusion that reverse causation is a plausible explanation for the association between exposure to talcum powder products and ovarian cancer. The principal presenting symptom is abdominal bloating, which does not appear to lead to more talc use.

conclusion that inflammation plays a role in increasing the risk of epithelial ovarian carcinoma. As stated by the National Cancer Institute, “Over time, chronic inflammation can cause DNA damage and lead to cancer. For example, people with chronic inflammatory bowel diseases…have an increased risk of colon cancer.” The time interval between inflammatory response and presentation of cancer can be many years. Animal studies, particularly, may show granulomatous or other inflammatory reactions while not necessarily demonstrating neoplastic changes due to the time interval required for cancer to develop.

Studies have shown that pelvic inflammatory disease and endometriosis (known to cause an inflammatory reaction) increase the risk of ovarian cancer (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Genofre et al. (2007) showed that talc can induce inflammation. Ness (1999) reported that inflammation of ovarian epithelium is a risk factor for ovarian cancer.

Inflammation has been implicated in carcinogenesis in several ways. Inflammation increases cytokines (Ness 1999). Shukla (2009) showed that nonfibrous talc can induce an inflammatory response that alters expression of genes in cancer pathways such as COX-2, ATF3, IL-6, and IL-8 in mesothelial cells. Further, inflammation increases oxidative stress (Ness 1999); Buz’Zard (2007) revealed that talc can induce oxidative stress and create reactive oxygen species (ROS), which in turn can induce ovarian neoplastic transformation in human ovarian cells. See also Saed (2017).

V. INFLAMMATION

Inflammation can produce toxic oxidants such as ROS that can be a source of mutagenesis to DNA. This damage to DNA by ROS is now accepted as a major cause of cancer, and has been demonstrated in ovarian cancer (Senthil 2004, Saed 2010, Saed 2017) as well as in breast and hepatocellular carcinoma (Waris 2006, Saed 2017). Talc exposure has been shown to cause a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), resulting in a decrease in cell viability and neoplastic transformation of ovarian cells. The authors concluded that “talc increased proliferation, induced neoplastic transformation and increased ROS generation time-dependently in the ovarian cells.” (Buz’Zard 2007)

Thus, it is accepted that inflammation causes oxidative stress. Oxidative stress leads to the formation of ROS and reactive nitrogen species (RNS). Oxidative stress is an important factor in the initiation and development of several cancers, including ovarian cancer (Senthil 2004, Saed 2010, Saed 2018). The production of oxidants and free radicals affects cellular mechanisms that control cell proliferation and apoptosis, which in turn play a role in the initiation and development of several cancers (Saed 2018). ROS and RNS can induce genetic mutations and DNA damage, thus causing oncogenic phenotypes. Additionally, oxidative stress affects transcription factors that modulate the expression of genes important to the development and metastasis of cancer cells (Saed 2018). Oxidative stress is also known to activate certain signaling pathways, which are critical for the initiation and maintenance of the oncogenic phenotype (Waris 2006). In fact, the major source of cellular ROS, the NAD(P)H

oxidase family of enzymes, has been linked to the survival and growth of tumor cells in pancreatic and lung cancers (Reuter 2010, Rojas 2016). Pro-oxidant enzymes such as myeloperoxidase (MPO), inducible nitric oxide synthase (iNOS), and NAD(P)H oxidase have been associated with initiation, progression, survival, and increased risk in cancers such as breast, ovarian, lung, prostate, bladder, colorectal, and melanoma (Lengyel 2010, Fletcher 2017, Saed 2017, Saed 2018). Angiogenesis is critical for the survival of solid tumors and is also regulated by ROS (Reuter 2010, Saed 2017). Thus, it is clear that alteration of oxidative balance can provide an environment for cancer cell survival (Saed 2018).

Gene point mutations resulting in single nucleotide polymorphisms (SNPs), or a variation in a single base pair in DNA, have been associated with oxidative DNA repair genes and redox genes with cancer susceptibility (Klaunig 2010). There is evidence that genetic polymorphisms in genes with anti-tumor activity are associated with cell cycle genes and play a role in ovarian cancer etiology (Goode 2009, Notaridou 2011). There are associations of specific SNPs in oxidant and anti-oxidant enzymes with increased risk and survival of ovarian cancer (Belotte 2015, Fletcher 2017).

Higher levels of oxidants have been described in epithelial ovarian cancer (Malone 2006, Saed 2010, Jiang 2011). Fletcher et al. published an abstract in the March 2018 Reproductive Sciences that showed talc can generate a pro-oxidant state in both normal ovarian epithelial and ovarian cancer cells. In this study, there was a marked increase in mRNA levels of the pro-oxidant enzymes iNOS and MPO in talc treated ovarian cancer cell lines and normal ovarian epithelial cells, as compared to controls within 24 hours. There was also a marked decrease in the mRNA levels of the anti-oxidant enzymes catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase 3 (SOD3), but a marked increase in glutathione reductase (GSR) and no change in glutathione S-transferase (GST) in the talc treated ovarian cancer cell line and in normal ovarian epithelial cells compared to controls within 24 hours (Fletcher 2018). In addition to tumorigenic cells generating high levels of ROS that activate signaling pathways which promote proliferation, it is known that tumorigenic cells maintain a high level of antioxidant activity to prevent buildup of ROS to levels that could induce tumor cell death (Schieber 2014, Saed 2017).

ROS and RNS are normally neutralized by enzymes such as SOD, CAT, GST, glutathione (GSH), thioredoxin coupled with thioredoxin reductase, glutaredoxin, glutathione peroxidase (GPX), and GSR (Lei 2016). Glutathione S-transferase is involved in detoxification of carcinogens by catalyzing their conjugation to GSH (Lei 2016). The GS-X-MRP1 efflux pump, which removes toxins from cells, is known to be stimulated by the GSH/GSSG complex and this process has been investigated as a mechanism for the development of tumor chemoresistance (Ishikawa 1993, Circu 2012).

Further, data demonstrates that talc exposure caused a statistically significant increase in ROS in ovarian polymorphonuclear neutrophils (PMNs), which resulted in a decrease in cell viability and neoplastic transformation of ovarian cells (Buz'Zard 2007).

Additionally, inflammation induces increased cellular proliferation, giving rise to potential DNA replication errors. This is one of the ways increased lifetime ovulations increase the risk of epithelial ovarian carcinomas. Studies have shown that ovulation results in an inflammatory response to disruption of the ovarian epithelium with the release of inflammatory mediators that initiate cellular transformation and growth (Richards 2002). Endometriosis causes an inflammatory reaction (including macrophage activation, cytokine release, and expression of growth factors) and is a risk factor for clear cell (Figure 4) and endometrioid (Figure 5) ovarian carcinomas (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Edwards 2015). Studies have also shown that pelvic inflammatory disease (PID) is an ovarian cancer risk factor (Risch 1995, Brinton 1997, Ness 2000, Brinton 2004, Kobayashi 2007, Lin 2011, Zhou 2017). Several prospective studies suggest that elevated serum levels of inflammatory markers such as CRP, TNF-α and IL-6 are predictive of development of ovarian cancer (McSorley 2007, Lundin 2009, Clendenen 2011, Toriola 2011, Poole 2013, Trabert 2014, Gupta 2016).

There also are some studies showing a protective effect of anti-inflammatory drugs on the risk of developing carcinoma, although some studies have failed to show a protective effect (Wu 2009). An analysis of many randomized controlled studies did show a reduced risk of developing carcinoma with aspirin use (Rothwell 2012). A 2014 article specifically evaluating ovarian carcinoma analyzed pooled data from 12 population-based case-control studies and showed a reduction of ovarian cancer risk with frequent aspirin and high-dose non-steroidal anti-inflammatory (NSAID) use (Trabert 2014). This further supports the role of inflammation in carcinogenesis, as this effect cannot be explained by other etiologies (Baandrup 2013, Trabert 2014).

Talc is not an inert substance. It has been shown to cause inflammation. Studies have shown increases in markers of inflammation following talc exposure (Allaire 1989, Genofre 2007, Arellano-Orden 2013). Talc is used therapeutically for patients with recurrent pneumothorax and pleural effusions based upon its ability to induce inflammation and adhesions. Injecting talc into the pleural space causes an inflammatory and granulomatous reaction, causing fibrosis and scarring which prevents further pneumothorax development (Antonangelo 2006, Najmunnisa 2007). This is mediated through the release of cytokines and chemokines (Nasreen 1998, van den Heuvel 1998), and the production of basic fibroblast growth factor (bFGF) (Antony 2004). It is worth noting that asbestos fibers are also known to initiate an inflammatory and scarring process within the pleura and peritoneum, which can eventually lead to neoplastic transformation of the mesothelium. The time interval between the initial inflammatory response for asbestos and talc and the development of cancer can be many years. Remote exposure will not necessarily mean there will be evidence of current inflammation or foreign body reaction when tissues are examined.

There also is evidence that talc induces macrophage TNF-α expression (Cheng 2000). Macrophages that express TNF-α promote ovarian tumorigenesis (Hagemann 2006). TNF-α is involved in chronic inflammation and induces mutations in vitro (Yan 2006). TNF-α induced chromosomal mutations occur mostly in cells with p53 aberrations (Yan 2006). Of note, high grade serous carcinomas typically have inactivating mutations in p53. Both talc and TNF-α induce macrophage expression of IL-8 (Nasreen 1998, van den Heuvel 1998), which attracts

neutrophils that then release ROS. This in turn causes a feedback loop between ROS generation and increased TNF-α expression, causing increased DNA damage (Xie 2000). This is an important line of biological experimental evidence supporting my causation opinion. The strongest association of talc and ovarian cancer is with invasive serous carcinomas, which commonly have p53 mutations, and TNF-α induced chromosomal mutations occur mostly in cells with p53 aberrations. Talc has been shown to induce macrophage TNF-α expression, which has been shown to promote ovarian tumorigenesis.

VI. ROLE OF IMMUNE SYSTEM IN CARCINOGENESIS

Studies have evaluated the protective role of the immune system in carcinogenesis, and in particular anti-MUC1 antibodies (Cramer 2005). MUC1 is a high molecular weight transmembrane protein expressed in many normal organs in a highly-glycosylated form. In cancer, including ovarian carcinoma, MUC1 is expressed at high levels in a poorly-glycosylated form. Anti-MUC1 antibodies are produced when high levels of the poorly-glycosylated form of MUC1 present to the immune system. Anti-MUC1 antibodies have been found in some cancers (Ho 1993, Dong 1997, Feng 2002) and have been associated with improved prognoses (Kotera 1994). Chronic processes including endometriosis, ovulation and talc exposure affect expression of MUC1 (Cramer 2005, Vlad 2006, Terry 2007). Decreased anti-MUC1 antibody production caused by these processes plausibly leads to immune-tolerance of an early ovarian carcinoma. Cramer et al. published a paper in 2005 that showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). Factors that decrease anti-MUC1 antibodies, such as incessant ovulation, have been associated with an increased risk of ovarian carcinoma (Terry 2007). Prospective data from the Nurses' Health Study (NHS) showed that tubal ligation increases anti-MUC1 antibodies, potentially by the procedure triggering the production of anti-MUC1, thus indicating another way tubal ligation exerts its protective effect. The study also showed that increased numbers of ovulatory cycles decrease anti-MUC1 antibodies, providing an explanation for the increased risk of ovarian cancer with increased lifetime ovulations (Pinheiro 2010). These studies provide evidence that MUC1 antibodies serve a role in the mechanism of and immune response in ovarian carcinogenesis. Because talc use is associated with a decrease in MUC1 antibody expression, the above is relevant to assessing the risk of talc use and ovarian cancer and provides further evidence supporting causation.

VII. COSMETIC TALC

Cosmetic talc has been used for decades, applied directly or indirectly to the genital region because of its high absorbency and softness (Langseth 2008).

Talc is a magnesium silicate hydroxide, characterized by water molecules in between silicate sheets. Asbestos is also a silicate mineral, but is somewhat morphologically distinct from talc and belongs to different silicate mineral groups. However, the chemical similarity of asbestos and talc led some researchers to postulate that both talc and asbestos could be causes of ovarian cancer (Graham 1967, Henderson 1971, Longo 1979). Early research into the possible link between talc and ovarian cancer was also instigated due to the fact that high

grade serous carcinoma, a type of invasive serous epithelial ovarian cancer (Figure 1), shown to be most commonly associated with perineal talc use, has striking morphologic similarities to mesothelioma (Figure 2), the tumor most associated with asbestos (Graham 1967). High grade ovarian serous carcinoma and mesothelioma express similar immunohistochemical markers, most notably cytokeratin pattern, WT-1 and calretinin. In fact, a great deal of surgical pathology literature deals with the nuances in differentiating peritoneal mesothelioma from high grade serous carcinoma. In the last few years, additional immunohistochemical panels have been developed that help distinguish between these two tumors (Laury 2010, Ordonez 2013), including PAX8, which is also expressed in fallopian tube epithelium. The morphologic and immunohistochemical similarities between asbestos and talc malignancies constitute another line of evidence supporting my opinion that talc exposure in the genital area causes ovarian cancer. Later in this report, I address the evidence that asbestos exposure can cause ovarian cancer.

VIII. TALC MIGRATION, TRANSLOCATION, INHALATION, AND LYMPHATIC TRANSPORT

In order for cosmetic talc applied to the perineum to reach the ovary or fallopian tube and exert a neoplastic effect, it needs to travel up through the vagina and uterus. It is known that substances can travel proximally through the female genital tract to the fallopian tubes and ovaries (Egli 1961, Venter 1979). Several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and even in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). This is evidence that talc can be transported through the lymphatic system. Thus, another biologically plausible pathway is inhalation leading to lymphatic transport to the ovaries (Suzuki 1991, Marchiori 2010, Frank 2011).

There is evidence that serous ovarian cancers are actually of fallopian tube origin (Piek 2003, Kindelberger 2007, Kurman 2010, Erickson 2013). When considering whether talcum powder can cause ovarian cancer, this consideration is not critical. Talcum powder particulates reach both the fallopian tubes and ovarian surfaces by migrating proximally.

IX. TALC IN TISSUE

As mentioned above, several studies have demonstrated the presence of talc in ovarian tissue (Henderson 1971, Henderson 1979, Mostafa 1985, Heller 1996) and one study found talc in the pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc (Cramer 2007). In Cramer et al.'s 2007 paper, the methods used by Dr. John Godleski to identify talc particles in tissue are outlined (Cramer 2007).

Tissue was first analyzed using polarized light microscopy to identify birefringent particles within the tissue plane. Polarized light microscopy is used in routine practice in anatomic pathology. One of the most common uses in surgical pathology is for the identification of calcium oxalate calcifications in breast tissue. In some lesions of the breast,

ranging from benign to malignant, calcifications occur that can be a marker for disease and are discovered on breast mammography. After mammography reveals calcifications and the radiologist determines them to be suspicious for disease, the area with calcifications is biopsied. The biopsy sample is then X-rayed to confirm the presence of the calcifications, and then submitted to the pathology laboratory for histologic analysis and diagnosis. The pathologist correlates the calcifications seen under the microscope with those in the specimen X-ray to be sure the calcifications the radiologist identified are visualized in the tissue sample. Calcium oxalate is a certain type of calcification that is not easily seen on light microscopy. If there appears to be a discrepancy between the tissue under light microscopy and the specimen X-ray (lack of calcifications under light microscopy), the pathologist will use polarized light microscopy to help identify calcium oxalate crystals, which are birefringent. Similarly, Dr. Godleski used polarized light microscopy to identify birefringent material that could be further analyzed using SEM and EDX.

SEM was more commonly used in surgical pathology before immunohistochemical studies were routinely used and before the common availability of molecular testing. However, SEM is still routinely used as an important diagnostic tool in areas of pathology in which immunohistochemical studies and molecular testing are less helpful, such as medical renal pathology, neuromuscular disorders and rare tumors. SEM uses electrons for imaging, analogous to light microscopy using light. SEM allows for much greater magnification (>100,000X) than light microscopy.

EDX is a qualitative and quantitative chemical analysis used in conjunction with SEM. It detects X-rays emitted from the sample during electron scanning to determine the elemental composition of the particle being examined. EDX is widely used in many biomedical areas, as it provides precise information on the chemical composition of subcellular structures that can be correlated with their SEM images (Wyroba 2015).

In Cramer et al 2007, the authors analyzed four pelvic lymph nodes from a 68 year old woman with ovarian papillary serous carcinoma and a small component of clear cell carcinoma. She had been a daily talc user for 30 years, having applied it to underwear and sanitary napkins. The lymph nodes showed birefringent particles via polarized light microscopy and were then analyzed by SEM and EDX. This showed magnesium and silicate signatures consistent with talc (Cramer 2007). Of note, there are similar studies performed with asbestos fibers in tissue sections (Roggli 1983, 1986).

Additionally, studies have shown Raman microscopy can be used to identify talc spectra in routinely processed, but unstained, histologic pathology specimens. Raman microscopy uses laser light to elicit the chemical and microstructural characterization of materials (Campion 2018).

Although the presence of talc particles found in ovarian cancer tissue does not prove that the talc played a causal role, when considered with the other lines of evidence supporting causation discussed in this report, the presence of talc in ovarian cancer tissue is certainly consistent with causation and provides additional evidence in support of a causal relationship between talcum powder products and ovarian cancer.

X. EPIDEMIOLOGICAL DATA REGARDING TALC USE AND OVARIAN CANCER:

As detailed below, there is consistent evidence from multiple observational studies, pooled analyses, and meta-analyses that exposure to talcum powder products is associated with an increased risk of ovarian cancer. When combined and considered with the biological evidence described above, this consistent epidemiologic data from multiple studies provides strong evidence that the association is, in fact causal.

Although occasional studies have not found talc powder applied to the perineum or contraceptive diaphragms[4] to be a significant risk for developing ovarian cancer, as detailed below, most have found an association, and the cumulative evidence from these studies, when considered with the other lines of evidence discussed above, provides strong and compelling evidence of a causal association.

XI. CASE-CONTROL STUDIES

Henderson first observed talc particles embedded in both ovarian tumors and normal ovaries (Henderson 1971). The first epidemiologic study on genital talc use and the risk of ovarian cancer was a case-control study by Cramer et al. (Cramer 1982). In this study, 215 women with epithelial ovarian cancer and 215 age-matched controls were questioned about talc use on the perineum and/or on sanitary napkins; 42.8% of ovarian cancer patients reported regular use of talc (prior to developing ovarian cancer) compared to 28.4% of controls, with an odds ratio (OR) of 1.92 (95% confidence level (CI) 1.27-2.89). The greatest risk in this study occurred in women who had used talc powder both directly on their perineum and on sanitary napkins compared to women who had no history of talc powder use; the odds ratio was 3.28 (CI 1.68-6.42). Of note, Cramer et al. did not exclude women from the control group who had a history of hysterectomy or other “pelvic surgeries” if the patient had intact ovaries by self-report. This could potentially lead to an underestimate of the risk of talc and ovarian cancer, as the controls may have had other confounding factors. They did control for confounding factors such as age, parity, religion, education, age of menarche, oral contraceptive use, hormone replacement therapy and smoking history.

While case control studies may have limitations with selection bias, Cramer et al. state “Our sample of cases represents more than 50% of ovarian cancer cases diagnosed

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[4] It is likely that studies based on talc with diaphragm use are generally limited to use by women for birth control purposes. This will not capture use before or after the women’s use of diaphragms for contraceptive purposes, a potential of multiple years that will not be captured in the study. Even for the years when women are using diaphragms, it is likely they are not using diaphragms for birth control on a daily basis. Therefore, diaphragm studies are likely to be biased toward the null; i.e., likely to understate talc exposure, and for that reason are likely to fail to detect an association that actually exists or understate the magnitude of risk.

in Boston residents in the study period. Therefore, it is difficult to conceive of a plausible bias in the selection of cases that would yield this excess use of talc." (Cramer 1982)

In additional to the Cramer 1982 study, numerous other case-control studies addressing talc use and ovarian cancer have shown statistically significant odds ratios greater than 1, indicating talc use is associated with an increased ovarian cancer risk (Harlow 1989, Booth 1989, Harlow 1992, Chang 1997, Cook 1997, Green 1997, Godard 1998, Cramer 1999, Gertig 2000, Ness 2000, Mills 2004, Merritt 2008, Wu 2009, Moorman 2009, Rosenblatt 2011, Kurta 2012, Houghton 2014, Wu 2015, Schildkraut 2016, Cramer 2016).

In a 1983 letter to the editor in JAMA in response to the 1982 Cramer study, Hartge and Hoover state that they found an association between genital talc use and ovarian cancer with a RR of 2.5, but the sample size was small (7 cases to 3 controls), resulting in a wide confidence interval (0.7-10.0). They did not find an association between ovarian cancer and body talc use or talc use on diaphragms, but again the sample sizes were small (Hartge 1983). Similarly, a study published by Tzonou et al. in 1983 showed no association between perineal talc use and ovarian cancer (RR 1.05; CI 0.28 to 3.98) but the frequency of reporting talc use was low in the study population, thus the wide CI (Tzonou 1983).

Whittemore et al. published a case-control study in 1988 that showed a RR of perineal talc use and ovarian cancer of 1.40, with a p value of 0.06. They did not see an increased risk of ovarian cancer in women who used talc on sanitary napkins or diaphragms. They did see an increased risk of ovarian cancer in women who used perineal talc for 1 to 9 years compared to those who used it for a shorter period (RR 1.60, p=0.05, CI 1.00-2.7) but did not see an increase with perineal talc users greater than 10 years (RR 1.11, p=0.61, CI 0.74-1.65). A strength of this study is that participants were not only asked about their history of talc use, but also about their history of cigarette smoking, coffee and alcohol consumption, thus addressing recall bias. A possible limitation of this study is the fact that the control group was a combined group of two separate control groups: one hospital based from the hospitals where the cases were admitted, and one community based. It was not described for what conditions the hospital controls were admitted (Whittemore 1988).

In 1989 Booth et al. published a study that showed an increased risk of ovarian cancer in daily talc users (RR 1.3, CI 0.8-1.9) and weekly talc users (RR 2.0, CI 1.3-3.4) as opposed to monthly (RR 0.7, CI 0.3-1.8) and rare (RR 0.9, CI 0.3-2.4) users. There were limitations of this study, however; participants were limited to women younger than 65 who had been diagnosed within the two years prior to interview. The data was adjusted for age in 5 year stratas and socio-economic status, but socio-economic status was based upon husband's career if married and participant's career if never married. Strengths, however, included queries of hormone replacement therapy, type of contraceptive use, and duration of oral contraceptive use; this helps to address recall bias. Additionally, hospital-based controls admitted for gynecologic disease and breast cancer,

among other diseases, were excluded and hospital admission diagnoses were listed (Booth 1989).

Harlow's 1992 study included 235 women with epithelial ovarian cancer and compared them to 239 control women matched for age, race and residence. After adjusting for age, parity, weight, education, marital status, religion, use of sanitary napkins and douching, it was found that talc use increased the ovarian cancer risk by 50% (OR=1.5, CI 1.0-2.1). Harlow's 1992 study also involved a dose-response effect; duration and frequency of perineal talc use was calculated into lifetime talc applications. Lifetime application ORs, when compared to control women with no perineal talc exposure, were 1.3 for <1000 (CI 0.7-2.7), 1.5 for 1000-10,000 (CI 0.9-2.4) and 1.8 for >10,000 (CI 1.0-3.0) (Harlow 1992). A dose response effect is a consideration in assessing causation. Harlow, Terry (2013) and Wu (2015) studies provide clear evidence of a dose effect. Particular strengths of the Harlow study are the number of potential confounding factors adjusted for and the detailed history on type of use and duration of use. Women with body exposure (non-genital) were considered non-exposed. Additionally, in the Harlow study, women were also asked about dietary and smoking histories, which helps to address potential recall bias.

Rosenblatt et al. published a study in 1992 that showed an increased risk of ovarian cancer with talc use (OR 1.7, but a small sample size with CI 0.7-3.9) (Rosenblatt 1992). In the Rosenblatt study, participants were also asked about oral contraceptive use and hormone replacement therapy, which helps to address potential recall bias. Another study published in 1992 by Chen et al. evaluated the association between talc use and ovarian cancer in a Beijing population. They found a RR of 3.9 in women with a history of use greater than 3 months, but the sample size was small with a 95% CI of 0.9-10.63. They also included dusting powder to the lower abdomen as well as perineum (Chen 1992), which would likely understate the magnitude of the association.

A 1997 study published in the journal *Cancer* by Chang et al. analyzed 450 patients with either ovarian borderline tumors or invasive ovarian carcinomas and showed an increased risk of tumor in women with either direct perineal application of talc or talc use on sanitary napkins (OR=1.42 after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, length of breastfeeding after pregnancy, and family history of ovarian cancer CI 1.08-1.86). For invasive ovarian carcinomas, the adjusted OR was 1.51 (CI 1.13-2.01). For borderline tumors, the adjusted OR was 1.24 (CI 0.76-2.02) (Chang 1997). The authors found that a borderline-significant association between duration of talc exposure and risk (OR 1.09, 95% CI 0.98-1.21, per 10 years of exposure). No significant association was found between frequency of exposure and risk. In comparing invasive and borderline carcinomas, risk remained elevated for both carcinoma types. The study did not assess for non-genital talc use. A particular strength of this study is that the same questions regarding talc use were asked about cornstarch use; they found no significant risk of ovarian cancer with cornstarch use (OR 0.31, CI 0.06-1.66), although only 1% of the populations reported using cornstarch (Chang 1997). Still, this helps to reconcile potential confounding risk factors of ovarian cancer in people more likely to use perineal powder. The interviews with participants also included taking

histories on oral contraceptive use and hormone replacement therapy, which helps to address recall bias.

Cook et al. also published a study in 1997 that evaluated 313 women with epithelial ovarian tumors (both invasive and borderline) and 422 controls. Only white women were included. They found that there was an increased risk of ovarian cancer with direct perineal powder dusting of 60% (OR=1.6, CI 1.1-2.3) and 90% (OR=1.9, CI 1.1-3.1) for genital deodorant sprays sprayed directly onto the perineum. Lifetime number of talc applications provided evidence of dose-response: a statistically significant increased risk (OR=1.7, CI 1.0-2.9 for less than or equal to 500 applications, OR=2.6, CI 0.9-7.6 for greater than 500 applications). A strength of this study is that participants were asked about smoking and contraceptive use, which helps to address recall bias. A limitation of this data is that all types of powder were included, such as cornstarch, “baby powder,” “deodorant powder,” and “scented body/bath powder.” However, the authors state, “No specific type of powder used for perineal dusting, diaphragm storage, or on sanitary napkins was strongly related to ovarian cancer risk, although there was a suggestion of an elevated risk associated with any use of talcum powder and bath/body powders (RR = 1.6, 95 percent Cl 0.9-2.8, and RR = 1.5, 95 percent Cl 0.9-2.4, respectively).” (Cook 1997)

In 1997, an Australian study performed by The Survey of Women’s Health Study Group enrolled 824 women with epithelial ovarian tumors, both invasive and borderline, and 855 controls. They found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.7) after adjusting for age, parity, duration of oral contraceptive use, BMI, smoking, education and family history of ovarian cancer. The risk was lowest in women who had not applied talc to their perineum and had either a tubal ligation or hysterectomy (RR=0.6, CI 0.50-0.84) (Green 1997). Because tubal ligation limits transport of talc fibers to the ovary, this study, with a finding of a protective effect in women with tubal ligation, provides an important piece of additional evidence. Strengths of this study include high response rate (90% of cases and 73% of eligible controls) and the verification of past surgical procedures by contacting participants’ surgeons. Additionally, participants were asked questions about other potential exposures such as smoking histories and pelvic inflammatory disease, which helps to address recall bias. Limitations include a lack of data on quantity of talc use.

In 1999, Wong et al. published a paper that did not show a consistent association with talc powder and ovarian cancer, evaluated by length of use as follows: talc use for 1-9 years (OR 0.9; 95% CI 0.6, 1.5), 10-19 years (OR 1.4; 95% CI 0.9, 2.2), or more than 20 years (OR 0.9; 95% CI 0.6, 1.2). This was after adjustment for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy. However, this study would tend to understate the magnitude of an association with genital talc use because it included talc use on thighs as well as genitals. The study used hospital controls, which raises a question of whether the controls were comparable to the cases (Wong 1999).

As part of Cramer et al.'s 1999 study, 563 women with newly diagnosed epithelial ovarian cancer were compared to 523 controls, and showed that perineal talc users had a significantly increased odds ratio for epithelial ovarian cancer (OR=1.60, CI 1.18-2.15). The effect of talc use was even stronger for invasive serous carcinoma (OR=1.70, CI 1.22-2.39). This was after adjusting for age, parity, oral contraceptive use, body mass index and family history of breast or ovarian cancer. The higher risk for women with invasive serous carcinoma was replicated in other studies, and this is an important finding in these studies because of its specificity. In addressing potential recall bias, Cramer et al. state, "…recall bias seems more likely to affect exposures that have occurred over a short term than those that have occurred over a long term. Since average duration of talc use exceeded 20 years in both cases and controls in our current study, genital talc exposure may be less likely to be subject to recall bias… It also seems reasonable that selective recall would lead to cases reporting all types of talc exposure more frequently than controls, but our study found that cases did not report a significant excess of talc use in non-genital areas compared to controls. Finally, if recall accounted for the association, one would expect little variation in the odds ratios by histologic type of ovarian cancer…. Regarding potential bias from confounding, we found no evidence that genital talc exposure varied by key risk factors for ovarian cancer such as age, parity or [oral contraceptive] use and little variability of the association by these and other variables." (Cramer 1999)

Ness et al.'s 2000 study evaluated 767 women with ovarian epithelial borderline tumors and ovarian invasive cancer compared to 1367 controls. Consistent talc use, defined as at least once per month for six or more months, increased the ovarian cancer risk by 50% (OR=1.5, CI 1.1-2.0) when applied to the perineal area directly and increased the risk by 60% (OR=1.6, CI 1.1-2.3) when used on sanitary napkins. This is after adjusting for age, parity, tubal ligation, hysterectomy, duration of oral contraceptive use, breast feeding and family history of ovarian cancer (Ness 2000). One explanation of the increased risk of talc use on sanitary napkins is that sanitary napkins may keep a larger amount of talc closer to the vagina over the course of several hours, thus increasing the risk of entry to perineum, while talc directly applied to the perineum may more easily disperse, however, many studies have failed to show an increased risk in ovarian cancer in participants whose only exposure to talc was on sanitary napkins. The strengths of this study include addressing multiple confounding factors. No dose-response was found; weaknesses include that only duration information was available, and genital/rectal talc use durations reported were combined with duration of use on the feet. Additionally, women who used just once per month were categorized as a user. These weaknesses may cause an underestimation of risk, and may have accounted for the lack of dose-response found.

Mills et al. published a study in 2004 that evaluated the association between talc use and ovarian cancer among 256 cases of ovarian cancer as compared to 1122 controls. Women diagnosed with invasive epithelial ovarian cancer with a history of genital talc use had an increased risk of 51% (OR=1.51, CI 1.07-2.12). This increased risk increased to 77% (OR=1.77, CI 1.12-2.81) for women diagnosed with invasive serous carcinoma.

Dose-response effects were also found. Increasing frequency of use was associated with increasing risk; women who reported use 4–7 times per week had a 74% elevation in epithelial ovarian cancer risk (p for trend = 0.015). However, the risk decreased between the second and third categories of use (from “rarely to several times per month” and “1-3 times per week” at 1.34 (CI 0.87-2.08) to 1.16 (CI 0.74-1.81), respectively). Duration of use of talc was also associated with increased risk, although the risk peaked among those reporting 4–12 years of use and declined somewhat among those reporting longer duration of use (p for trend = 0.045). Cumulative use also demonstrated an uneven association with risk of epithelial ovarian cancer in that the point estimates peaked in the second and third quartiles of intensity but declined in the highest quartile of use. These findings were after adjusting for age, race/ethnicity, duration of oral contraceptive use and duration of breast feeding. Yet, there wasn’t adjustment for first relative history of breast or ovarian cancer, pregnancy history, parity, BMI, hysterectomy, tubal ligation or hormone replacement therapy; according to the authors, the Hosmer-Lemshow goodness-of-fit tests revealed that after terms for duration of oral contraceptive use and duration of breast-feeding were added to the models, fit was not improved by the addition of these variables, nor were the estimated odds ratios altered by the addition of several of these variables (Mills 2004). However, the fact that participants were queried about other possible exposures such as hormone replacement therapy helps to address potential recall bias.

In Wu et al.’s 2009 study, women were found to be at increased risk of ovarian cancer if they had a history of prior perineal talc use, with the risk increasing significantly in those with long term (20+ years) and frequent (at least daily) use with a relative risk of 2.08 (CI 1.34-3.23), i.e., a dose effect. The authors did find an increased risk in women who used talc on sanitary napkins (RR 1.61, CI 0.93-2.78), underwear (RR 1.71, CI 0.99-2.97) and diaphragms/cervical caps (RR 1.14, CI 0.46-2.87). There was a stronger association between talc use and serous ovarian cancer; the relative risk with any talc use was 1.70 (CI 1.27-2.28). Strengths of this study include the adjustment for multiple possible confounding factors (age, race/ethnicity, education, age of menarche, parity, oral contraceptive use, family history of ovarian or breast cancer, menopausal status and tubal ligation). Another strength was that participants were queried about NSAID and endometriosis histories, helping to address potential recall bias. The authors mention in their discussion that the participation response was “modest,” possibly leading to selection bias (Wu 2009).

Rosenblatt et al. published a study in 2011 that showed an overall increased risk of ovarian cancer in women who used talc after bathing (OR=1.27, CI 0.97-1.66) with a more pronounced risk in women diagnosed with mucinous borderline tumors (OR=1.78, CI 0.98–3.23) and serous borderline tumors (OR=1.47, CI 0.85-2.55) (serous borderline tumor illustrated in Figure 3). They did not see an increased risk by extent of use, defined as years in which powder was used, or as lifetime number of applications. There was no alteration in the risk of ovarian cancer associated with other types of powder exposure such as sanitary napkins or diaphragms. This study did not find an increased risk of invasive serous carcinoma (OR 1.01, CI 0.69-1.47). (Rosenblatt 2011) A strength of this

study is that participants were queried about other potential exposures (smoking, alcohol and endometriosis histories), which helps to address recall bias.

In 2012, Kurta et al. evaluated talc use and the risk of ovarian cancer, although their main focus of the study was the associated risk of ovarian cancer with fertility drug use. They found a OR of 1.40 (CI 1.16-1.69). Since talc was not the primary focus of this study, duration of use was not considered; participants were categorized as talc users if they had ever used talc versus never-users. Perineal talc use was only generally defined as dusting powder or deodorizing spray on the genital or rectal areas, sanitary napkins, underwear, or diaphragms or cervical caps (Kurta 2012). A strength of this study is that its main focus was on fertility drug use; participants were asked about exposures such as fertility treatments and hormone replacement therapy, which helps to address potential recall bias.

Wu et al. published a paper in 2015 that evaluated talc use and invasive ovarian cancer in white, Hispanic and African American women. They found that talc use was more common in African-American women (44.1%) than in non-Hispanic whites (30.4%) or Hispanics (28.9%) (p=0.001). The results showed ORs of 1.41 for white women (CI 1.21-1.67), 1.77 for Hispanic women (CI 1.20-2.62) and 1.56 for African American women, although the CI for African American women was 0.80-3.04. Overall, the OR was 1.46 (CI 1.27-1.69). However, the response rate and sample size for this study was somewhat small, and participants with less than one year of use were categorized as never users (Wu 2015).

In 2016, Schildkraut et al. published a paper as part of the African American Cancer Epidemiology Study (AACES), a case-control study of epithelial ovarian cancer in African American women. According to the authors, due to the relatively small number of women who reported having only used genital powder (43 cases and 44 controls), the authors merged this exposure category with those who reported use of both non-genital and genital powder, creating an exposure category of "any" genital powder use, but separately evaluated the categories as "only" or "any" genital powder use. They reported an increased risk of ovarian cancer in "any" genital powder users (OR=1.44, CI 1.11-1.86) and noted a statistically significant dose response effect for both duration of use and lifetime applications. A strength of this study was adjustment for multiple confounding factors such as age, education, BMI, parity, tubal ligation, OCP use, first degree relative with breast or ovarian cancer, and interview year (taking into account litigation cases in the year 2014). Participants were also asked about hormone replacement therapy, another potential exposure, thus helping to address potential recall bias. A weakness of this study is that participants were considered "regular users" if they reported using cornstarch, baby or deodorizing powders at least one time per month for at least 6 months, and "never users" if they did not, leading to possible misclassification that would bias toward the null (Schildkraut 2016).

The totality of the results of the case-control studies support a causal link between talc and ovarian cancer. When observational studies find an increased risk of disease with a certain exposure, the possible reasons are chance, bias, confounding and causation.

There is a general consistency of these individual studies; the ORs have been of similar magnitude in studies spanning different decades, in different populations, with different study designs, by different investigators, over different continents and with adjustment for multiple confounders. Therefore, the possibility that the association between perineal talc use and ovarian cancer is due to chance is extremely unlikely.

Although retrospective case-control studies potentially have an element of recall bias and other potential biases, again, the consistency of results across these studies and populations makes recall and other bias an unlikely explanation. During the period that the majority of studies were conducted, public awareness of the link between talc and ovarian cancer was limited. There is also a much stronger and statistically significant association of perineal talc use and ovarian cancer in studies that compared all-body talc use to perineal use. The finding in some studies that serous carcinoma has a stronger association with perineal talc exposure than other histologic subtypes of ovarian cancer also argues against recall bias, as participants are very unlikely to have knowledge about the histologic subtyping of ovarian cancer. In addition, in studies where participants are asked to recall multiple exposures, not just talc exposure, this will minimize the risk of recall bias because it is unlikely that participants will differentially recall talc exposure but not other exposures, especially if they are blinded to the study hypothesis. Studies using trained interviewers, structured interview questionnaires, and blinding of both study participants and the interviewers to the study hypotheses will also limit the potential for recall bias.

Selection bias (which can arise based on differential participation rates or other differences between comparison groups) accounting for the results across studies is also unlikely. To see such consistent associations between perineal talc use and ovarian cancer, there would need to be strong associations between participation and perineal talc use, and strong differences amongst cases and controls due to selection bias only - this would be extremely unlikely to produce such large biases across studies. Most studies adjusted for confounders, with the majority adjusting for age, BMI, and parity among others. With chance, bias, and confounding being unlikely explanations for the association of perineal talc use and ovarian cancer across multiple studies, this leaves causation as the most likely explanation.

XII. COHORT STUDIES

The talc literature includes several cohort studies reporting the relative risk for perineal talc use and risk of ovarian cancer, including the Nurses' Health Study, the Women's Health Initiative and the Sister Study (Gertig 2000, Gates 2008, Gates 2010 and Gonzalez 2016). There were several important limitations of these studies to adequately capture risk of ovarian cancer based on the methodology used by the researchers to assess talc exposure.

The Gertig study evaluated prospective cohort data from 78,630 women, and although there was a 12% overall increased risk of ovarian cancer in women with a history of daily genital talc use, this was not statistically significant. Yet, the investigators

reported a statistically significant increased risk of invasive serous carcinoma (RR=1.4, CI 1.02-1.91) after adjusting for age, parity, duration of oral contraceptive use, post-menopausal hormone use, tubal ligation, BMI and smoking (Gertig 2000). Additionally, the lack of statistical significance of overall ovarian cancer risk may be due to several important limitations with this study, including the fact that the question of talc use was only in one questionnaire in 1982 and did not include questions on duration of use. Thus, a person who used talc just a few times would be included with women who used talc daily over a long duration, and this will have the effect of understating the risk. In fact, in a follow-up 2008 report, Gates et al. noted that since talc exposure was only referred to once in questionnaires, it is possible that some participants were misclassified with respect to their talc use or that some women may have started talc use after 1982 and thus these women would not be included in the talc user group (Gates 2008). This would understate the risk and decrease the calculated statistical significance of talc-related ovarian cancer. An additional review of the Nurses' Health Study published by Gates et al. in 2010 studied 876 cases of ovarian cancer and talc use, although this was not the primary focus of the study. This study found an overall increased risk of ovarian cancer with talc use (RR=1.06), but found an increased risk for mucinous tumors (RR=1.50) (Gates 2010) (mucinous carcinoma illustrated I Figure 6). Again, the weaknesses in the study include the fact that talc use was only queried once in 1982, and the authors state themselves that the limited data on talc use may have influenced the observed association with ovarian cancer.

Cohort studies like the Nurses' Health Study, Women's Health Initiative Study and the Sister Study have some drawbacks when studying rarer diseases compared to case-control studies that have been described above. Cohort and case-control studies are both observational, and both have strengths and limitations. Cohort studies begin when all participants are free of the disease in question. After a follow-up period, those that have the disease being studied are compared by exposure risk being studied to those who did not develop the disease. Although this helps to ensure exposure predates disease, there may be a lack of data if the disease is rare or if there is a long latency period between exposure and disease presentation/diagnosis, as is the case of ovarian cancer and talc. In contrast, in case-control studies, patients already have the disease being studied and are compared to controls who do not have the disease with a focus on the rates of exposure to the agent of interest (here, talcum powder products) in the cases as compared to the controls. A possible limitation of case-control studies in the context of ovarian cancer and talc is the fact that exposure to talc is self-reported and subject to potential recall bias.

The case-control studies may unavoidably have recall bias, as talc use was self-reported by participants. In their 2018 meta-analysis discussed below, Penninkilampi et al. noted that in some studies, interviewers were not blinded to cases and controls and many studies did not describe whether their controls had a personal history of previous ovarian cancer. However, they also noted that in general, controls were well matched to cases by other possible confounding factors such as age, geographic, location and ethnicity (Penninkilampi 2018).

In the 2008 Gates paper, women with certain variants in glutathionine S-transferase M1 (GSTM1) and/or glutathionine S-transferase T1 (GSTT1) were shown to have a higher risk of talc-associated ovarian cancer. Glutathione S-transferases catalyze the conjugation of glutathione to numerous potentially genotoxic compounds. Individuals with homozygous deletions of GSTM or GSTT have reduced or no glutathione S-transferase activity and may be unable to eliminate electrophilic carcinogens as efficiently (Coughlin 2002). The 2008 Gates study included 1,175 cases and 1,202 controls from a case-control study and 210 cases and 600 controls from the prospective Nurses' Health Study. Participants were genotyped for the GSTM1 and GSTT1 gene deletions and three NAT2 polymorphisms. Regular talc use was associated with increased ovarian cancer risk in the combined study population (relative risk=1.36, CI 1.14-1.63; p-trend<0.001). In the pooled analysis, the association of talc and ovarian cancer was stronger among women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). There was no clear evidence of an interaction with GSTM1 alone or NAT2. Without talc exposure, these genes were not clearly associated with risk of ovarian cancer (Gates 2008). The specificity of the findings linking the genetic polymorphisms with ovarian cancer subtype most associated implicates yet another aspect of the Bradford Hill viewpoints.

As previously detailed, the Nurses' Health Study also showed that genital talc use was associated with lower levels of anti-MUC1 antibodies, which has been associated with an increased risk of ovarian cancer. As part of the Nurse's Health Study, Pinheiro et al. published a paper in 2010 that showed increasing anti-MUC1 antibody levels were associated with a nonsignificant trend for a lower risk of ovarian cancer with highly significant heterogeneity by age (p-heterogeneity=0.005). The authors concluded that anti-MUC1 antibodies evaluated several years prior to diagnosis may be associated with lower risk of subsequent ovarian cancer in women less than 64 years old at assessment (Pinheiro 2010). Cramer et al. 2005 study showed factors which increase the levels of anti-MUC1 antibodies lower the risk of ovarian carcinoma (Cramer 2005). These findings provide evidence that a plausible mechanism for talc-associated ovarian cancer is a down-regulated immune response to MUC1, and thus an immune tolerance of an emerging MUC1-expressing tumor.

The Women's Health Initiative Observational Study (WHI-OS) did not report a statistically significant increased risk of ovarian cancer with talc use (Houghton 2014). In that study, 61,576 women were enrolled and 429 developed ovarian cancer during follow-up. The study did find a 12% increased risk of ovarian cancer in perineal talc users (RR=1.12, CI 0.92-1.36), but it was not statistically significant. However, the risk of developing serous carcinoma was increased by 18% (RR=1.18, CI 0.89-1.56), and by 13% for invasive serous carcinoma (RR=1.13, CI 0.84-1.51). Additionally, 101 cases were categorized histologically as "other," including tumors that were self-reported, not validated and potentially may not have even been primary ovarian tumors. This would bias the risk estimate of talc use in ovarian cancer in this study toward the null by including cancers or other tumors potentially from other sites; in other words, non-specific cancer types may have been included that are not known to have an association with talc use. Another weakness of the study is that although the authors did evaluate the

effect of duration of use of genital talc on the risk of ovarian cancer, they did not evaluate frequency of use. Thus a woman who used talc for twenty years once a month would be treated the same as a woman who used it every day for twenty years. This will tend to understate or obscure the true risk of long term, frequent use. The study also was of an older age group (50-79) who were post-menopausal at time of enrollment, which adds selection bias.

Another study in which the effect of talc use on the risk of ovarian cancer is likely diluted or understated is the Sister Study, published by Gonzalez et al. in 2016. In this study, there was no reported association between perineal talc use and subsequent ovarian cancer. The study only enrolled women with a full or half-sister who had been diagnosed with breast cancer. BRCA1 and BRCA2 mutations are associated with a markedly increased risk of both breast and ovarian cancer, and in the Sister Study, women were not tested for this mutation. Most of the ovarian cancers associated with BRCA mutations are of the invasive serous subtype, the same subtype most strongly associated with talc use in prior studies. By not testing the women for the genetic mutation, the Sister Study analyzed a population of women with an increased risk of having a BRCA mutation (by having a first degree relative, or sister/half-sister, with breast cancer), a significant confounding factor that was not considered. Another limitation of this study is that the mean follow-up was 6.6 years, a very short period considering the generally long latency period of ovarian cancer. The Sister Study did find an increased risk in ovarian cancer in women who douched, providing evidence supporting the link between particulate route of access to the ovary/fallopian tube. The histologic subtype of the ovarian cancer was also not evaluated. Further, similar to the other cohort studies, the Gonzalez 2016 study failed to adequately capture both duration and frequency of talc exposure as participants were only asked if they used talc in the last 12 months.

XIII. META-ANALYSES REGARDING TALC USE AND OVARIAN CANCER:

Meta-analyses are an important tool that combines study results from multiple studies to develop a single result that has greater power to detect a more precise estimate of risk. Several meta-analyses have been published on the association between talc use and ovarian cancer, all showing an increased risk (Harlow and Cramer 1992, Gross and Berg 1995, Cramer and Harlow 1999, Huncharek 2003, Langseth 2008, Berge 2018, Penninkilampi 2018).

In 1992 Harlow and Cramer published combined results from six case-control studies of the association between talc use and ovarian cancer that were performed between 1982 and 1989. The association was statistically significant (OR=1.3, CI 1.1-1.6) (Harlow 1992). In 1995, Gross and Berg published a meta-analysis that included the six case-control studies evaluated in the 1992 Harlow and Cramer paper, plus three additional studies. This produced a statistically significant increased risk (OR=1.27, CI 1.09-1.48) (Gross 1995). Of note, this study was supported in part by Johnson and Johnson, raising the issue of funding bias.

Cramer published another meta-analysis in 1999 that included the nine studies in Gross and Berg's 1995 paper plus five additional ones performed through 1999. The overall risk of ovarian cancer in talc users was found to be increased at 36% (OR=1.36, CI 1.24-1.49) (Cramer 1999).

Huncharek et al. performed a meta-analysis in 2003 that added five new studies and included all of the previous studies except the 1983 Hartge and 1996 Shushan studies. The OR in this study was 1.33 (CI 1.16-1.45). Interestingly, the authors concluded that even with this statistically significant OR, the data "do not support the existence of a causal relationship" between talc use and ovarian cancer (Huncharek 2003). In a subsequent paper published by Huncharek et al., support from Johnson and Johnson and Luzanec America was acknowledged (Huncharek 2007), raising the issue of funding bias.

Langseth et al. published a comprehensive meta-analysis in 2008 of the risk of ovarian cancer associated with talc use. The combined OR was 1.35 (CI 1.26-1.46), and specifically 1.4 for population-based studies (CI 1.29-1.52), the less potentially biased type of study. Langseth et al. also noted that the risk of serous ovarian tumors in particular with talc use may be greater (Langseth 2008).

In 2016, Cramer published a retrospective case-control study that incorporated data from three enrollment phases (1992-1997, 1998-2002 and 2003-2008) and combined data from the Nurses' Health Study (Gates 2008) and data from participants in the Ovarian Cancer Association Consortium (OCAC, Terry 2013). The study found a statistically significant increased risk of invasive serous, invasive endometrioid and serous borderline ovarian tumors in women who were genital talc users, with the highest risk (OR=2.33 (CI 1.32-4.12) and OR=2.57 (CI 1.51-4.36) for pre- and postmenopausal women, respectively) with the greatest lifetime exposure, as defined by "talc-years," or number of applications per year multiplied by years of use. A dose-response was most prevalent for invasive serous carcinoma. This study is important as evidence supporting an association between talc and ovarian cancer as the authors analyzed case-control data collected over 16 years in 2,041 epithelial ovarian cancer cases and 2,100 age- and-residence-matched controls. As the authors state, they "addressed issues related to definition of the exposure, bias and confounding, effect modification, histologic heterogeneity, and dose-response. Talc used regularly in the genital area was associated with a 33% increase in ovarian cancer risk overall." (Cramer 2016)

Berge et al. published another meta-analysis in 2018 that found a summary RR of 1.22 (CI 1.13-1.30). They found that the association between talc and ovarian cancer was stronger in case-control studies (RR 1.26, CI 1.17-1.35) than cohort studies (RR 1.02, CI 0.85-1.20). The limitations of the cohort studies are discussed above; limitations of case-control studies are recall bias and selection bias. Addressing the latter, Berge et al. found a higher summary risk estimate in hospital-based case-control studies compared to community-based case-control studies, but this difference was not statistically significant. Recall bias can be present in case-control studies, however, Berge et al. found the greatest association between genital talc use and serous carcinoma (RR 1.24, CI 1.15-

1.34). This would argue against recall bias, as participants would likely not know the categorization of epithelial ovarian tumors, nor the fact that invasive serous carcinoma has been shown to have the strongest association in the majority of studies.

Penninkilampi et al. published a meta-analysis in 2018 that found any perineal talc use was associated with an increased risk of ovarian cancer (OR 1.31, CI 1.24-1.39). They found a dose-response effect with greater than 3600 lifetime applications (OR 1.42, CI 1.25-1.61) compared to less than 3600 lifetime applications (OR 1.32, CI 1.15-1.50). Similar to the Berge 2018 study, an association was found in the case-control studies (OR 1.35, CI 1.27-1.43) but not in the cohort studies (OR 1.06, CI 0.90-1.25). However, Penninkilampi et al. did find an association in cohort studies between talc use and invasive serous carcinoma (OR 1.25, CI 1.01-1.55). (Penninkilampi 2018)

XIV. POOLED STUDY REGARDING TALC USE AND OVARIAN CANCER:

The meta-analyses discussed above summarize previously published data and thus have increased statistical power for a more precise estimate of effect on talc in ovarian cancer risk (Cohn 2003). However, the strength of meta-analyses depends on the quality of the previously published data analysis. In comparison, a pooled study analyzes primary data from different studies/researchers. The Terry 2013 study is a retrospective pooled study from eight population-based case-control studies from OCAC. One advantage of pooled studies is the ability to include a large sample size; Terry et al. included 8,525 cases of ovarian, fallopian tube or perineal cancer and 9,859 controls. Some of the included OCAC studies had previously reported on powder use (Chang 1997, Cramer 1999, Merritt 2008, Moorman 2009, and Rosenblatt 2011), and according to Terry et al., three of these provided data for the pooled 2013 analysis that had not been included in the previous publications. The other three studies had not previously published their genital powder data (Goodman 2008, Lo-Ciganic 2012, Pike 2004). The pooled analysis showed an OR for genital talc use and epithelial ovarian cancer of 1.24 (95% CI 1.15-1.33) after adjustment for age, oral contraceptive use, tubal ligation, BMI and race/ethnicity (Terry 2013). This is consistent with the majority of meta-analyses and individual studies.

A strength of a pooled study versus a meta-analysis is that pooled studies have increased standardization. As an example, the Terry 2013 study excluded participants that data was not available on regarding tubal ligation, oral contraceptive duration, parity or height and weight. This adjusts for study-specific differences in confounding factors. A weakness of pooled studies is that they are limited by the methods of original data collection; for example, Terry et al. state "Limitations of our pooled analysis include differences in the wording of questions about genital powder use between studies and the retrospective nature of the exposure ascertainment." As Blettner (1999) stated, "Pooling decreases the variation caused by random error (increasing the sample size) but does not eliminate any bias (systemic errors)." In the 2013 Terry et al. study, classification between cases and controls differed between studies, as the women who were classified as genital powder users varied from "ever" use, "ever regular" use, to powder use for at least one year. However, Terry et al. conclude that if anything, this led to an underestimate of the true association for any given

study "[due to the fact that] exposure definitions are the same for cases and controls within each study, misclassification of genital powder exposure due to the question wording would be nondifferential…." (Terry 2013).

XV. ASBESTOS, TALCUM POWDER PRODUCTS, AND OVARIAN CANCER:

I have seen evidence that talcum powder products manufactured by Johnson & Johnson (J&J Baby Powder and Shower to Shower) contained and continue to contain asbestos, talc containing asbestiform fibers (e.g. talc occurring in a fibrous habit) heavy metals (such as cobalt, chromium, nickel) and fragrance chemicals (Longo et al. 2017 and 2018, Blount 1991, Blount Deposition 2018, Hopkins Deposition and Exhibit 2018, Pier Deposition and Exhibit 2018). Other than cobalt, which has been identified as a "possible" carcinogen, all of these constituents have been identified as known carcinogens by IARC (IARC 2012). It should be noted that National Institute for Occupational Safety and Health (NIOSH) has determined that "there is no safe level of asbestos exposure for any type of asbestos fiber" (NIOSH 1980). As part of my review and consideration of the evidence I have also reviewed Dr. Michael Crowley's opinion that "fragrance chemicals in Johnson & Johnson talcum powder products contribute to the inflammatory properties, toxicity, and potential carcinogenicity of the products." The presence of these constituents as part of the talcum powder product provides additional evidence of biological plausibility for talcum powder products to cause ovarian cancer.

Asbestos is a silicate mineral in polyfilamentous bundles. Other silicate minerals exist, such as talc, but asbestos is classified by its flexible fibers with small diameter and large length. The forms of asbestos are serpentine silicates ("sheet silicates") such as chrysotile, and amphibole silicates ("chain silicates") such as crocidolite, amosite, anthophyllite, actinolite, and tremolite (IARC Monograph). The carcinogenic properties of asbestos fibers depend on the length of the fiber (Stanton 1972) and its chemical composition, structure, and cell environment (Mossman 1998, Robledo 1999, IARC Monograph). Asbestos fiber surface reactivity with free radical generation has also been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph).

It has long been generally accepted that asbestos exposure causes mesothelioma and lung cancer (Dement 1994, deKlerk 1996, Berry 2000). Approximately 125 million people around the world have been exposed to asbestos in work environments, and at least 90,000 people die each year from asbestos-related lung cancer, mesothelioma, or asbestosis (Burki 2009). The relationship between asbestos exposure and ovarian cancer had been less studied; however, in 2009, the IARC Monograph Working Group concluded that there is sufficient evidence to show that asbestos exposure can cause ovarian cancer (Straif 2009, IARC Monograph).

In the late 1960's, a suggested link between talc and ovarian cancer was made for the following reasons: first, talc powders were shown to contain asbestos (Cralley 1968); second, intraperineally placed asbestos in animals induced a proliferation of the ovarian mesothelial lining from one layer to multiple layers (Graham 1967). Of note, it was tremolite asbestos that was used by Graham, the same type of amphibole asbestos that is found in asbestos-contaminated talc. It is important to note that similar to talc being found on the ovarian surfaces of perineal talc users, asbestos fibers have been found in women whose household contacts worked with asbestos and in Norwegian paper and pulp workers (Heller 1996, Langseth 2007).

In 1972, Newhouse et al. published a study of the mortality of female asbestos workers and found at least 4 deaths due to ovarian cancer compared to an expected number of 0.6. During histological review of some of the pathology samples from these workers, there was evidence that another two deaths that had been registered as due to carcinomatosis were likely caused by ovarian cancer (Newhouse 1972).

Ten years later in 1982, Wignall et al. published a study that followed 535 women who were assembly workers that had direct crocidolite exposure during the manufacturing of military gas masks. The authors found 2 deaths due to ovarian cancer in women that were employed at the facility for less than 1 year, with a standardized mortality rate (SMR) of 1.77. Two ovarian cancer deaths occurred in women with a 1 year history of employment at the facility (SMR=2.11) and one ovarian cancer death in a woman with a 3 year history of employment (SMR=1.05). The authors noted that the expected number of deaths is low, making stable estimates of SMR difficult. However, the authors conclude that the "excess of deaths from carcinoma of the ovary was unexpected at the start of the study but appears to be related directly to exposure to asbestos" (Wignall 1982).

Also published in 1982 was a study by Acheson et al. that evaluated two groups of women exposed to asbestos who assembled gas masks in two separate facilities: 570 women at Blackburn (civilian respirators that contained chrysotile) and 757 women at Leyland (military respirators containing crocidolite). The study found a SMR in the crocidolite group for ovarian cancer of 2.75 (CI 1.42-4.81) and a SMR of 1.48 (CI 0.48-3.44) for the chrysotile group. The authors noted that the risk of ovarian cancer increased over time for up to 40 years post exposure (Acheson 1982).

A 1994 study by Rosler et al. examined mortality from ovarian cancer in a cohort of 616 women in Germany who had been occupationally exposed to asbestos. Although about 95% of asbestos used in Germany was chrysotile, the authors noted that they could not exclude a mixture containing crocidolite. Two deaths from ovarian cancer were observed, compared to an expected 1.8 (SMR 1.09, CI 0.13-3.95). (Rosler 1994).

In 1999, Germani et al. published a study of ovarian cancer mortality in 631 women workers in Italy who had been compensated for asbestosis. They found a total of nine ovarian cancer deaths (SMR 4.77, CI 2.18-9.04) which included four deaths in a subset of asbestos-textile workers (SMR 5.26, CI 1.43-13.47) and five deaths in the subset of asbestos cement workers (SMR 5.40, CI 1.75-12.61). (Germani 1999).

Also in 1999, Vasama-Neovonen et al. published a case-control study of ovarian cancer and occupational exposure in Finland. The Standardized Incidence Ratio (SIR) was 1.30 (CI 0.9-1.80) between ovarian cancer and "medium/high levels of asbestos," and the SIR was 1.1 (CI 0.8-1.3) for "low levels of asbestos." The SIR is obtained by dividing the observed number of cases of cancer by the expected number of cases in the general population. The type of asbestos fiber was not noted (Vasama-Neovonen 1999).

Again in 1999, Langseth et al. published a study of 4247 workers employed for at least one year between 1920 and 1993 in the Norwegian pulp and paper industry. 85% of them were paper or administration workers. The follow-up period for cancer was from 1953-1993. An excess risk of ovarian cancer was found (SIR = 1.50, CI 1.07-2.09). The SIR was highest among those younger than 55 years, and mostly among those working in paper departments. The type of asbestos fiber was not specified (Langseth 1999). Langseth et al. published a follow-up case-control study in 2004 that examined the association between asbestos exposure and ovarian cancer in this same cohort of female pulp and paper workers in Norway that had been found to have excess morbidity from ovarian cancer. In the case-control study, the odds ratio for occupational exposure to asbestos based on 46 cases of ovarian cancer was 2.02 (CI 0.72-5.66), although this was not statistically significant (Langseth 2004).

In 2000, Berry et al. published a study that evaluated the mortality of a cohort of over 5000 London asbestos factory workers, both men and women, who were followed for over 30 years since first asbestos exposure. The study classified exposure by degree (low, moderate and severe) and duration (2 years or less or more than 2 years). They assessed mortality by comparing the number of cohort deaths with the number of expected deaths in England and Wales based on sex, age and period. The study found that there was a significant increase of ovarian cancer in women with severe exposure for more than 2 years (SMR of 5.35) and an overall SMR for all exposure lengths of 2.53 (CI 1.16-4.8) (Berry 2000).

In 2005, Pira et al. published a cohort study of 1077 women with at least a one month history of employment between 1946 and 1984 at an asbestos-textile factory in Italy. A variety of asbestos types were used in this facility, including crocidolite. They followed up with the cohort in 1996. There were five deaths due to ovarian cancer with an overall SMR of 2.61 (CI 0.85-6.09), but there was a SMR of 5.73 for women with longer employment histories at the facility (greater than or equal to 10 years of employment). Among women with greater than or equal to 35 years since first employment exposure, the SMR was 5.37 (Pira 2005).

Also in 2005, Wilcsynska et al. published a study of 1470 Polish asbestos cement factory workers with a follow-up period from 1945 to 1999 and a SMR of ovarian cancer among workers of 3.76 (CI 1.38-8.18). The type of asbestos fiber was not specified (Wilcsynska 2005).

McDonald et al. published a study in 2006 that followed 567 people, mostly women, who had assembled gas masks in the Nottingham factory between 1940 and 1944 and showed

a SMR for ovarian cancer of 1.2 (CI 0.6-2.2). Gas masks assembled at this facility had filter pads that contained 20% crocidolite. As an aside, this study found that the first deaths due to mesothelioma happened a little more than 20 years after exposure, which is consistent with most other studies (McDonald 2006) and highlights the lengthy time interval between exposure and presentation of disease in asbestos-related mesothelioma.

In 2008 Reid et al. published a study of 2552 women and girls who lived in a Western Australia mining town between 1943 and 1992 where crocidolite asbestos was mined. They were not directly involved in mining but there was extensive environmental contamination of the town. They found a SMR for ovarian cancer of 1.52 (Reid 2008).

Reid et al. published a study in 2009 that followed the same cohort of 2552 women and girls in Western Australia with environmental exposure to crocidolite asbestos and added 416 women to the study that had worked in the Wittenoom crocidolite asbestos mines and mills. For the latter group, there wasn't an increased rate of ovarian cancer (SIR of 0.49, CI 0.01-2.74), but the authors noted that the "female Australian Blue Asbestos workers at Wittenoom mostly worked in the company offices, shop, and hotel. Their occupational exposure was unlikely to have been as high as that reported for women in the earlier cohorts, which may explain why no excess risk for ovarian cancer was observed" (Reid 2009).

Pukkala et al. published a study in 2009 on the incidence of ovarian cancer in women employed in various occupations in Denmark, Finland, Iceland, Norway and Sweden. One of the groups examined were plumbers, who are known to have occupational exposure to asbestos. Four ovarian cancers were found in this group of plumbers, with a Standardized Incidence Rate (SIR) of 3.33 (CI 0.91-8.52). Fiber type was not specified (Pukkala 2009).

Magnani et al. and Bertolotti et al. published studies in 2008 that followed the same cohort of former asbestos-cement workers who were employed at a facility in Casale Montferrato, Italy. A mix of crocidolite and chrysotile asbestos was used at this factory. They observed nine ovarian cancer deaths versus 4 expected (SMR of 2.27). In women who had 30 or more years of exposure, the SMR was 2.97 (Magnani 2008, Bertolotti 2008). Ferrante et al. published a study in 2007 that examined cancer mortality in the household contacts of men who worked at this facility; among women with exposure due to household contacts, there were 11 ovarian cancer deaths versus an expected 7.7, or SMR of 1.42 (CI 0.71-2.54). (Ferrante 2007).

I am aware of two meta-analyses, both published in 2011, that evaluated a link between asbestos and ovarian cancer. The first was published in 2011 by Reid et al. and analyzed fourteen cohort and two case-control studies of women with exposure to asbestos in their work environment. The majority of the cohort cases they evaluated are detailed above. The authors added a 2002 paper by Szeszenia-Dabrowska et al. that studied Polish women diagnosed with asbestosis and a 2004 paper by Mamo et al. that studied Turin asbestos textile factory workers (Szeszenia-Dabrowska 2002, Mamo 2004). The two case-control studies they evaluated were a 1992 study of Johns Hopkins patients by Rosenblatt et al. and a 2004 study

of Norwegian pulp and paper workers by Langseth et al., the same group of workers previously described above. Reid et al. concluded that although women "thought to have ovarian cancer" (not all cases of ovarian cancer were histologically reviewed and confirmed) had an increased rate if exposed to asbestos, the overall numbers were still small and further study was warranted as one misclassification could skew the data (Reid 2011).

The authors of the second 2011 meta-analysis, Camargo et al., included 18 studies. They did not include the 1992 Rosenblatt et al. study or the 2004 Langseth et al. study but added six others: a 1986 study of cement workers in the U.K. by Gardner et al., a 1989 study of friction material workers in the U.K. by Newhouse et al., a 2007 study of textile workers in the U.S. by Hein et al., a 2009 study of textile workers in the U.S. by Loomis et al., and two other 2009 studies by Harding et al. and Clin et al. The authors of this second meta-analysis came to a stronger conclusion that the findings were consistent with an association between asbestos exposure and an increased risk of ovarian cancer (Carmargo 2011).

Considering the consistency of these studies, the Bradford Hill viewpoints (strength of association, consistency, biological plausibility, etc.) and the well-known carcinogenic properties of asbestos, it is my opinion to a reasonable degree of scientific certainty that asbestos exposure can cause ovarian cancer. Even disregarding the evidence that cosmetic talc is contaminated with asbestos, it is my opinion that talc is causally associated with ovarian cancer. However, to the extent that talcum powder products contain even small amounts of asbestos, the evidence of causation is even more compelling.

XVI. BRADFORD HILL ANALYSIS:

In 1965, Sir Austin Bradford Hill proposed nine viewpoints of a causal relationship: strength of association, consistency, specificity, temporality, biologic gradient, plausibility, coherence, experiment and analogy (Hill 1965). It is important to remember, however, as discussed at the beginning of this report, that Hill himself noted that none of these viewpoints of association – including the existence of a statistically significant relationship – is either necessary or sufficient to show causation. There are no "hard-and-fast rules". Rather, the totality of the evidence must be weighed and considered. With that important command in mind, let us examine the evidence.

1. Strength of association:

Strength of association is often measured by the magnitude of the relative risk (CDC). All meta-analyses and pooled analyses have found a statistically significant increased risk of ovarian cancer in perineal talc users, with relative risks falling between 1 and 2. This is consistent with a causal relationship. Strength of association is higher for asbestos. There are a number of examples of causal relationships where the relative risk is less than 2.0 (e.g., second hand smoke and lung cancer, oral contraceptive use and breast cancer, radon exposure and lung cancer). It also is worth noting that small or moderate effects on the benefit side can have important clinical significance. For example, aspirin has been deemed "causal" of cardiovascular event reduction, based on multiple studies that reported a benefit between 20-30% reduction in cardiovascular events. The strength of this association, especially combined

with the consistency, weigh in favor of a cause-and-effect relationship between talc and ovarian cancer.

2. Consistency:

The statistically significant increased risk of ovarian cancer with talc use has been consistent in size across multiple studies, different populations, different investigators, multiple countries and over time. Hill stressed the importance of repetitive findings; no single study can prove or disprove causation due to possible inherent internal validity issues. The consistency of the increased risk of ovarian cancer (and in particular invasive serous carcinoma) with talc use found in numerous studies, in different countries, and after adjustments for confounding factors cannot be disregarded. There also is consistent evidence of an association between asbestos and ovarian cancer. This was a very important factor in my analysis.

3. Specificity:

Hill suggested that associations are more likely to be causal when they are specific, in other words, a particular substance causes a single disease. However, in the half-century experience has shown that this aspect of causation is not particularly important in the context of cancer. Few examples of specificity are found when it comes to cancer. Smoking is generally accepted to be a cause of lung cancer, yet smoking is also associated with COPD, heart disease, stroke, and asthma, amongst other diseases. In multiple studies, talc has been shown to be associated with epithelial ovarian cancer, with invasive serous ovarian cancer showing the strongest association. Asbestos is generally accepted to cause mesothelioma, lung cancer, and ovarian cancer. Asbestos is also generally accepted to cause asbestosis/pulmonary fibrosis, pleural inflammation and thickening. This was a less important factor in my analysis.

4. Temporality:

Exposure to a substance must precede onset of disease for it to be causal. The above-described case-control and cohort studies had the objective of assessing talc exposure that preceded the onset of disease. In cohort studies, the exposure data was obtained before any women were diagnosed with ovarian cancer. In the case-control studies, women with ovarian cancer reported exposures prior to their diagnosis and controls reported exposures in the same time frame. In many studies the exposures went back several decades, providing even more assurance that the temporality requirement is met. This was an important factor in my analysis.

5. Biological gradient:

A biologic gradient, or dose-response, refers to an increased exposure corresponding to an increased risk. In the case of talc exposure, dose-response would ideally include both frequency of use and duration of use, or “application years” (total lifetime applications) similar to “pack-years” used in the setting of smoking. However, application-years is much more difficult to assess than pack-years, since one cannot easily quantify the amount of talc

used during each perineal application (unlike in smoking, where one can easily count the number of cigarettes smoked to calculate pack-years). Yet, when studies have evaluated duration and frequency of perineal talc use, most have found an increased risk of ovarian cancer with increased exposure (Harlow 1992, Cramer 1999, Mills 2004, Merritt 2008, Wu 2009, Terry 2013, Penninkilampi 2018). In the case of asbestos and mesothelioma, a study published by Plato et al. in 2018 found "a significant, dose–response relationship between maximum intensity asbestos exposure and mesothelioma of the pleura and cumulative asbestos exposure with 30-, 40-, and 50-years lag time. Cumulative exposure to asbestos, even at low levels, entailed an increased risk of mesothelioma of the pleura, indicating that even short periods with cumulative doses <1.78 f-y/ml can increase the risk of mesothelioma. Time since first exposure did not show any sufficient dose–response relationship in the longest lag period (>50 years)." (Plato 2018)

While there is evidence of a dose response, this data is more equivocal because of the challenge in measuring and comparing the extent of talcum powder usage. The evidence of biological gradient for talcum powder products is therefore very difficult to study. The evidence of biological gradient supports cause and effect, but for the reasons noted, it is limited by difficulties in the measurement of exposure. This was an important factor in my analysis.

6. Plausibility:

In this context, plausibility means that an association can be explained by and is consistent with existing scientific knowledge and, in particular, that there is a biologically plausible explanation for the exposure (to talc) as a cause of ovarian cancer. Thus, plausibility is dependent upon the current state of scientific knowledge regarding a mechanism of disease. Hill noted plausibility is helpful but limited by current knowledge.

There is evidence that validates the biological plausibility of talc-related ovarian cancer. It is generally accepted that inflammation plays a role in carcinogenesis. Pelvic inflammatory disease and endometriosis are known risk factors for ovarian cancer, and they cause the release of inflammatory mediators. Talc is known to produce an inflammatory reaction, and is in fact used in clinical practice to induce inflammation in the pleura to treat patients with pneumothorax and pleural effusions. It has also been demonstrated that particles, including talc, can migrate proximally through the female genital tract and gain access to the perineum, ovaries, and fallopian tubes. Thus, it is plausible that talc can reach the ovaries and fallopian tubes and cause a proinflammatory reaction, including induction of cytokines and ROS that play a role in the onset of ovarian cancer. Other plausible mechanisms include a down-regulated immune response to MUC1, causing an immune tolerance of a MUC1-expressing cancer, and talc-induced macrophage TNF-α expression and subsequent ovarian tumorigenesis. The 2008 Gates study showed an association of talc and ovarian cancer in women with the GSTT1-null genotype (p-interaction=0.03), particularly in combination with the GSTM1-present genotype (p-interaction=0.03). It is thus plausible that women with a GSST1-null phenotype are unable to eliminate talc as efficiently and are at increased risk of ovarian cancer. It is also highly plausible that asbestos in asbestos-tainted talc also releases cytokines and mutagenic ROS from inflammatory cells.

In the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). Asbestos-derived free radicals can lead to a variety of effects on cells including lipid peroxidation, DNA oxidation, TNF release, cell apoptosis, and increased uptake of asbestos fibers (Mossman 1983, Hobson 1990, Ghio 1998, Churg 1998, Gulumian 1999, Aust 1999, Upadhyay 2003, IARC Monograph). Asbestos fibers may directly cause the generation of ROS (IOM 2006) and indirectly cause ROS by inducing inflammation and macrophage activation (IARC Monograph). As noted above, the carcinogenicity of the other constituents of talc (cobalt, chromium, nickel, and fragrance ingredients) adds strength to biologic plausibility.

This biologic evidence, provides a biologically plausible explanation for the increased risk seen in the epidemiologic studies and is therefore a very strong factor in favor of a cause and effect relationship.

7. Coherence:

Coherence in this context means coherence between epidemiological and generally accepted knowledge of the disease in question. Numerous studies addressing talc use and ovarian cancer have indicated talc use increases ovarian cancer risk consistently. The coherence of the epidemiological evidence linking a risk of ovarian cancer with talc use, in tandem with biologically plausible mechanistic evidence discussed above, is striking and weighs heavily in support of causation.

8. Experiment:

Hill suggested that evidence drawn from experimental manipulation, particularly epidemiologic studies in which disease risk declines following an intervention or cessation of exposure, may lead to the strongest support for causal association. No studies exist that follow women after cessation of genital powder use and assess them specifically for a change in risk of ovarian cancer. The challenge of such a study is that it has been shown that talc-associated ovarian cancer takes years or decades before onset of disease. However, the Australian study performed by The Survey of Women's Health Study Group published in 1997 found that the risk of ovarian cancer was highest among women who were talc users and had not undergone surgical sterilization (RR=1.3, CI 1.1-1.6). (Green 1997). This indicates that tubal ligation or hysterectomy, by impeding the proximal migration of talc into the perineum to the ovaries and fallopian tubes, decreases the risk of talc-associated ovarian cancer, lending support to Hill's experiment aspect in the context of talc and ovarian cancer.

There are experimental studies in the literature that support a causal relationship between talc and ovarian cancer. Examples include studies that show increases in inflammatory markers following talc exposure (Allaire 1989, Genofre 2009, Arellano-Orden 2013). There is also evidence that talc causes neoplastic transformation in ovarian cells (Buz'Zard 2007) and that talc induces genotoxicity in mesothelial cells (Shukla 2009). Additionally, there is evidence that talc induces macrophage TNF-α expression (Cheng 2000), and macrophages that express TNF-α have been shown to promote ovarian tumorigenesis

(Hagemann 2006). Of note, invasive serous carcinomas commonly have p53 mutations and TNF-α induced chromosomal mutations have been shown to occur mostly in cells with p53 aberrations (Yan 2006).

It has long been generally accepted that asbestos exposure causes mesothelioma, ovarian cancer, and lung cancer (Dement 1994, deKlerk 1996, Berry 2000, IARC 2012). The experimental evidence was very important to my analysis.

9. Analogy:

Comparisons of similar associations can be used to determine plausibility. Hill suggested that when there is strong evidence of a causal relationship between a particular agent and a specific disease, researchers should be more accepting of weaker evidence that a similar agent may cause a similar disease. Analogy under the Bradford Hill viewpoints has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way (Susser 1991). In the case of talc and ovarian cancer, one can use the analogy of asbestos and mesothelioma. Both talc and asbestos are silicates, and asbestos causes an inflammatory and fibrosing reaction within the pleura, which is generally accepted to be the primary cause of mesothelioma years later. It is the inflammatory and fibrosing reaction caused by talc that has led to its common use in the treatment of pneumothorax and pleural effusions by injection into the pleural cavity. Similarly, in the case of asbestos, fiber surface reactivity with free radical generation has been accepted as a mechanism of carcinogenesis (IARC Monograph). The analogy evidence was somewhat important in my analysis.

XVII. CONCLUSION:

Based upon the totality of the evidence and consideration of the Bradford Hill viewpoints, which includes the high consistency and replication of the findings in the epidemiological studies, pathological, biological, and mechanistic evidence, it is my opinion, which I hold to a reasonable degree of scientific and medical certainty, that genital talcum powder exposure can cause ovarian cancer.

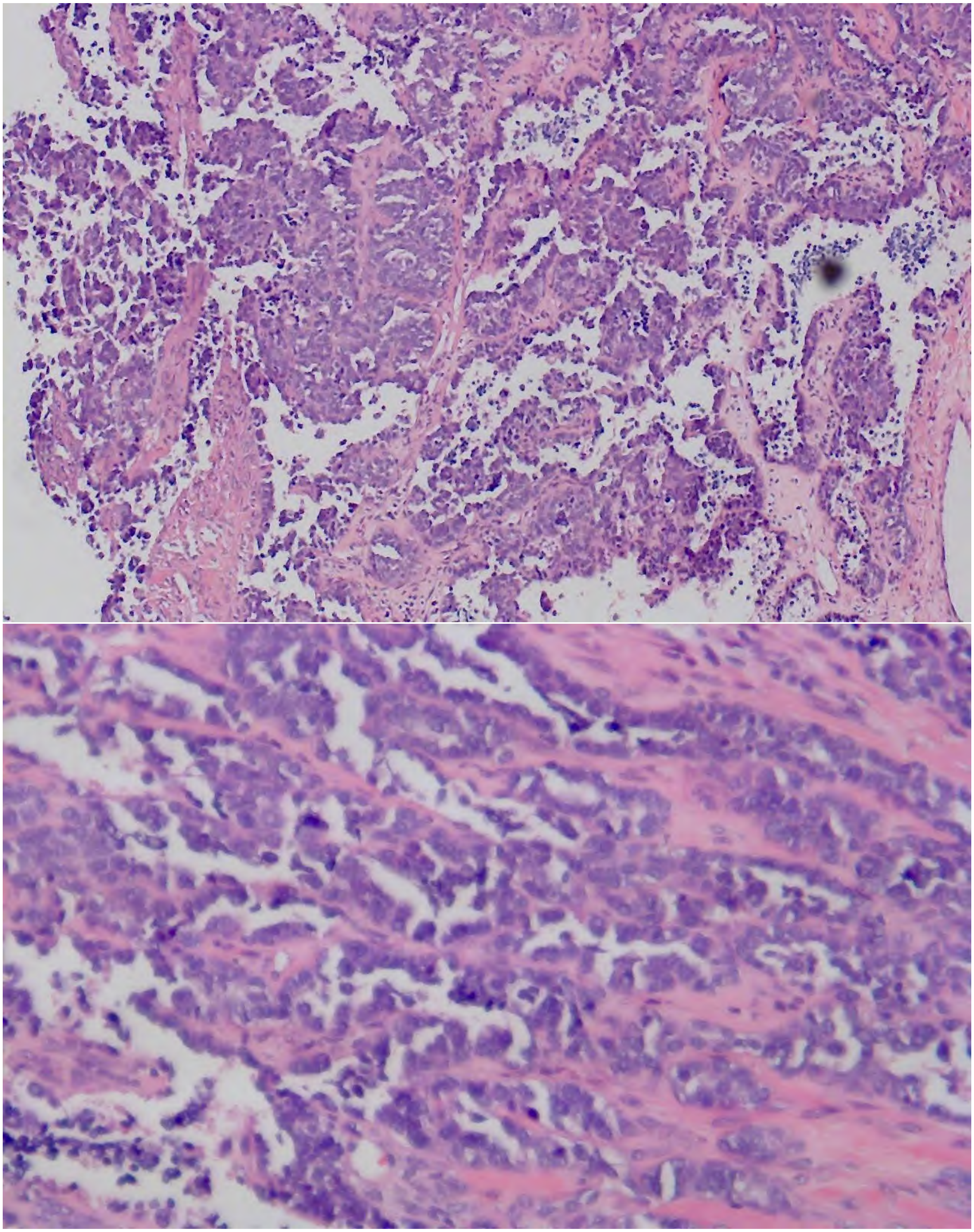

Figure 1. Ovarian invasive serous carcinoma.

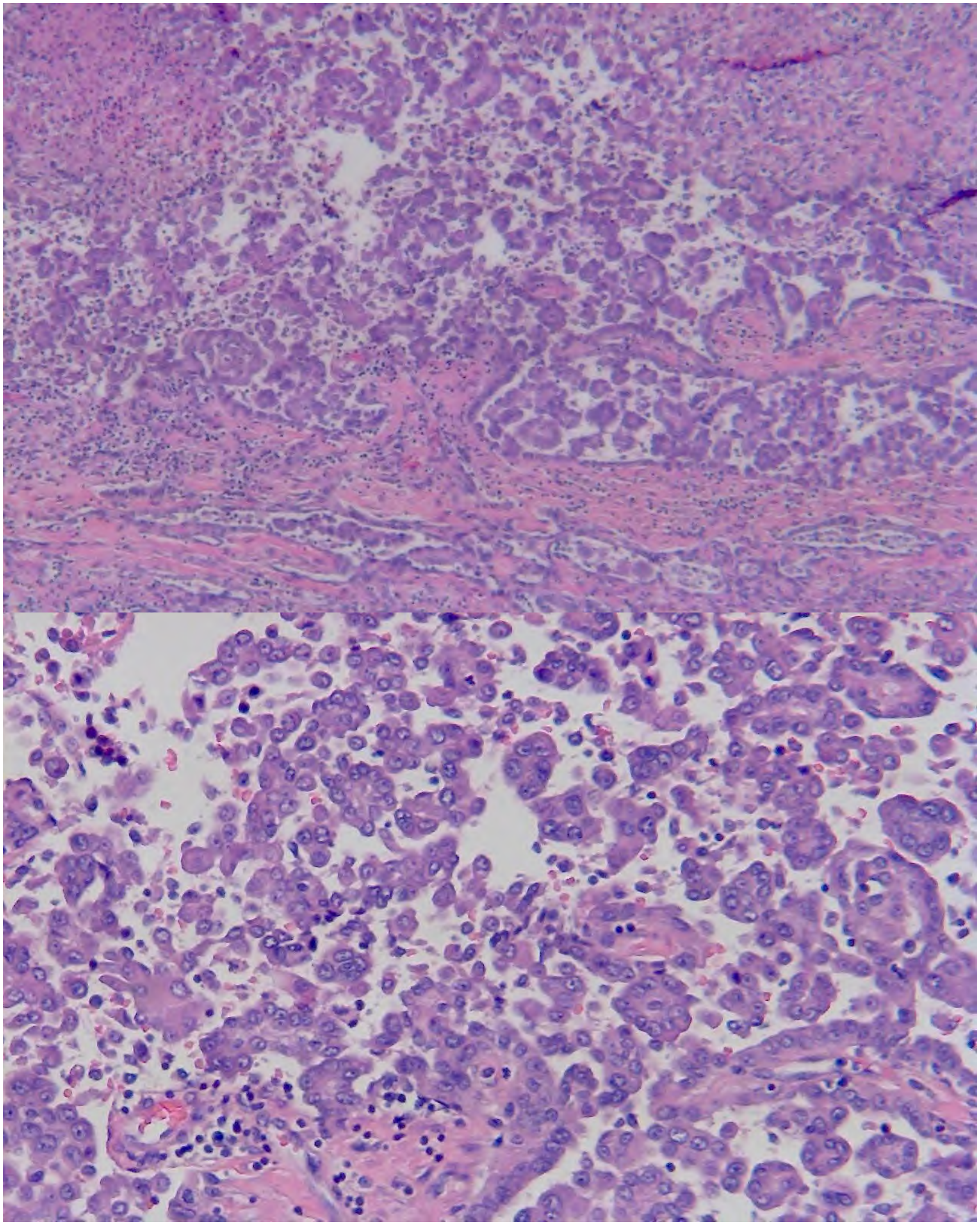

Figure 2. Mesothelioma. Notice the morphologic similarities to ovarian serous carcinoma (Fig 1).

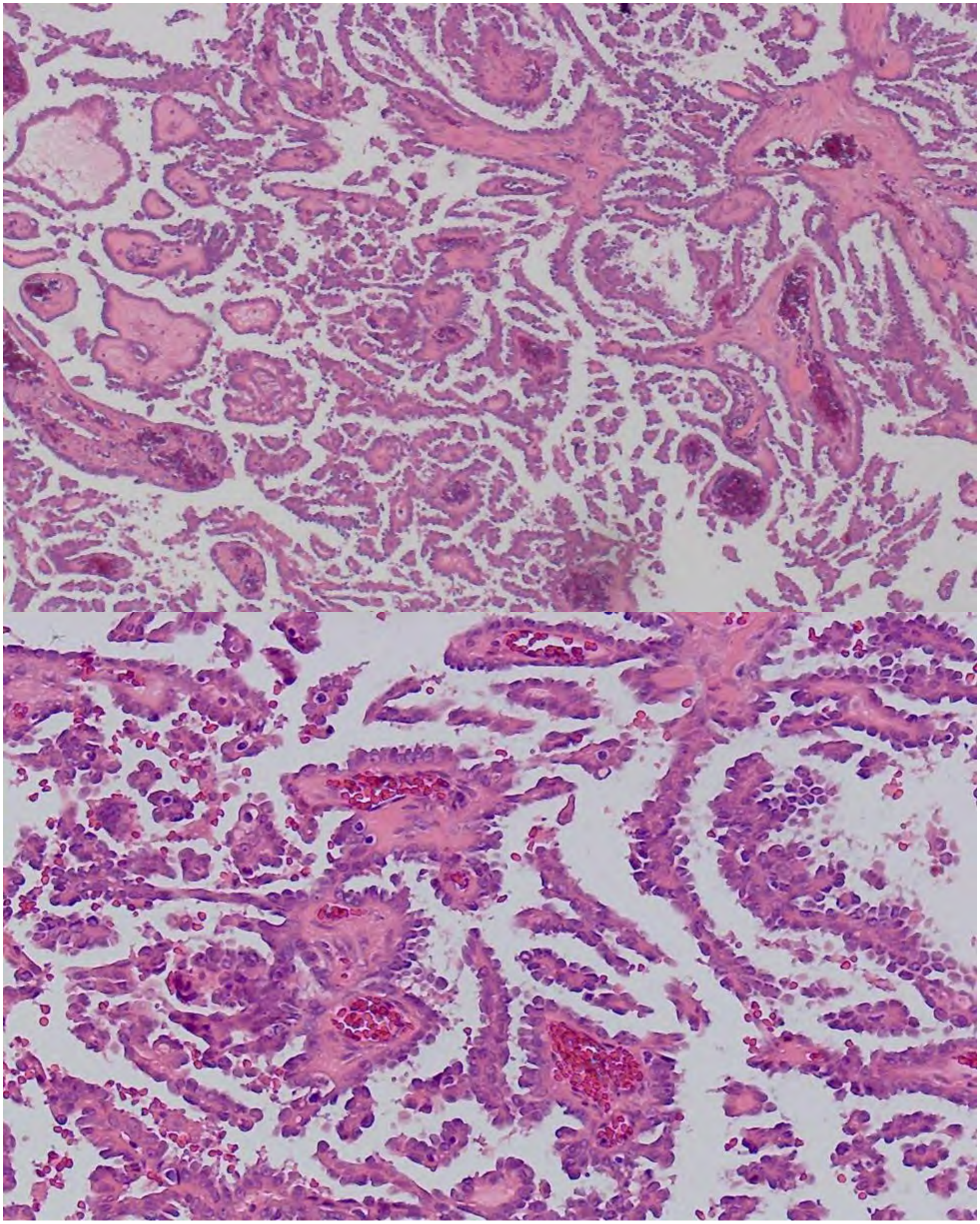

Figure 3. Ovarian serous borderline tumor.

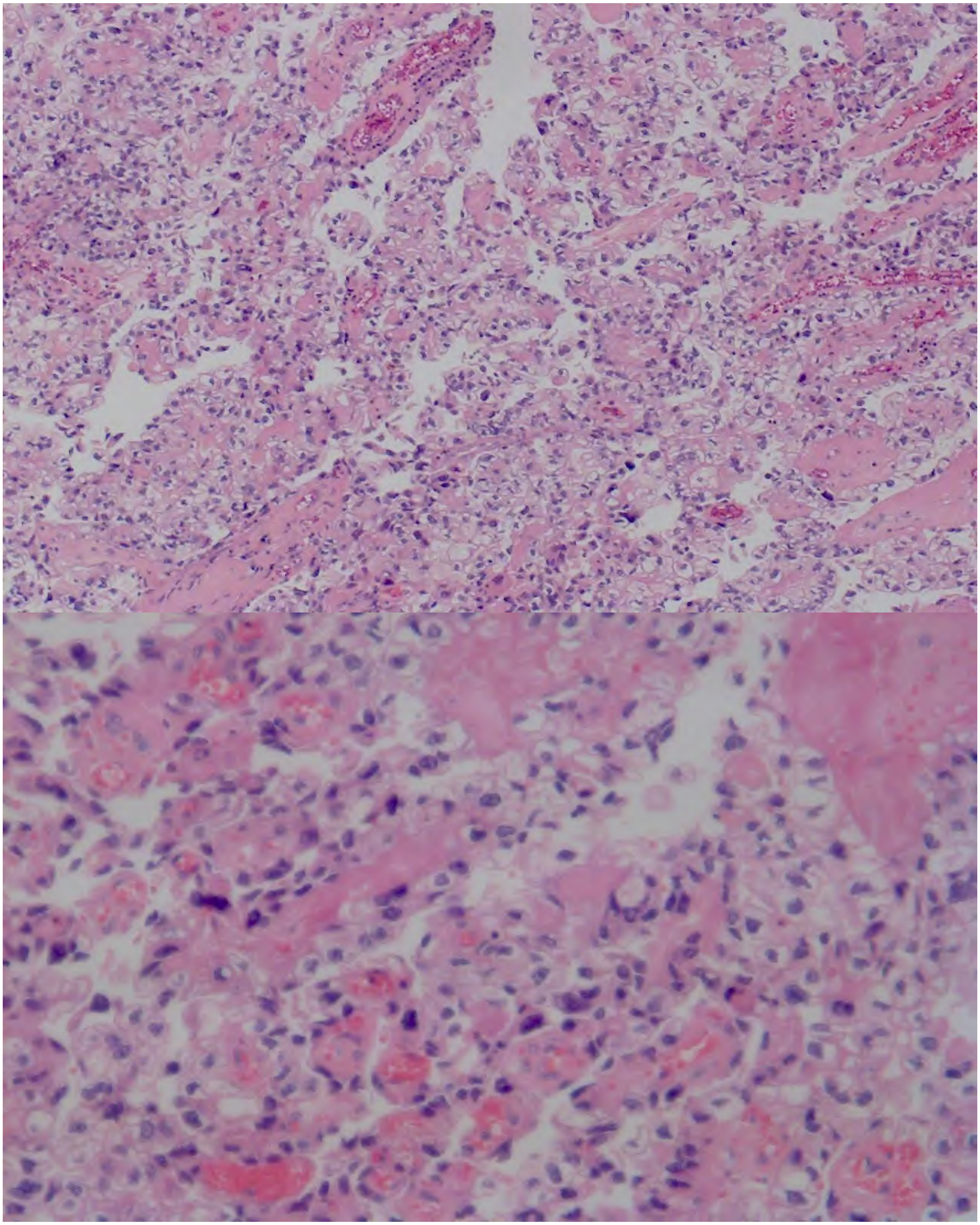

Figure 4. Ovarian clear cell carcinoma.

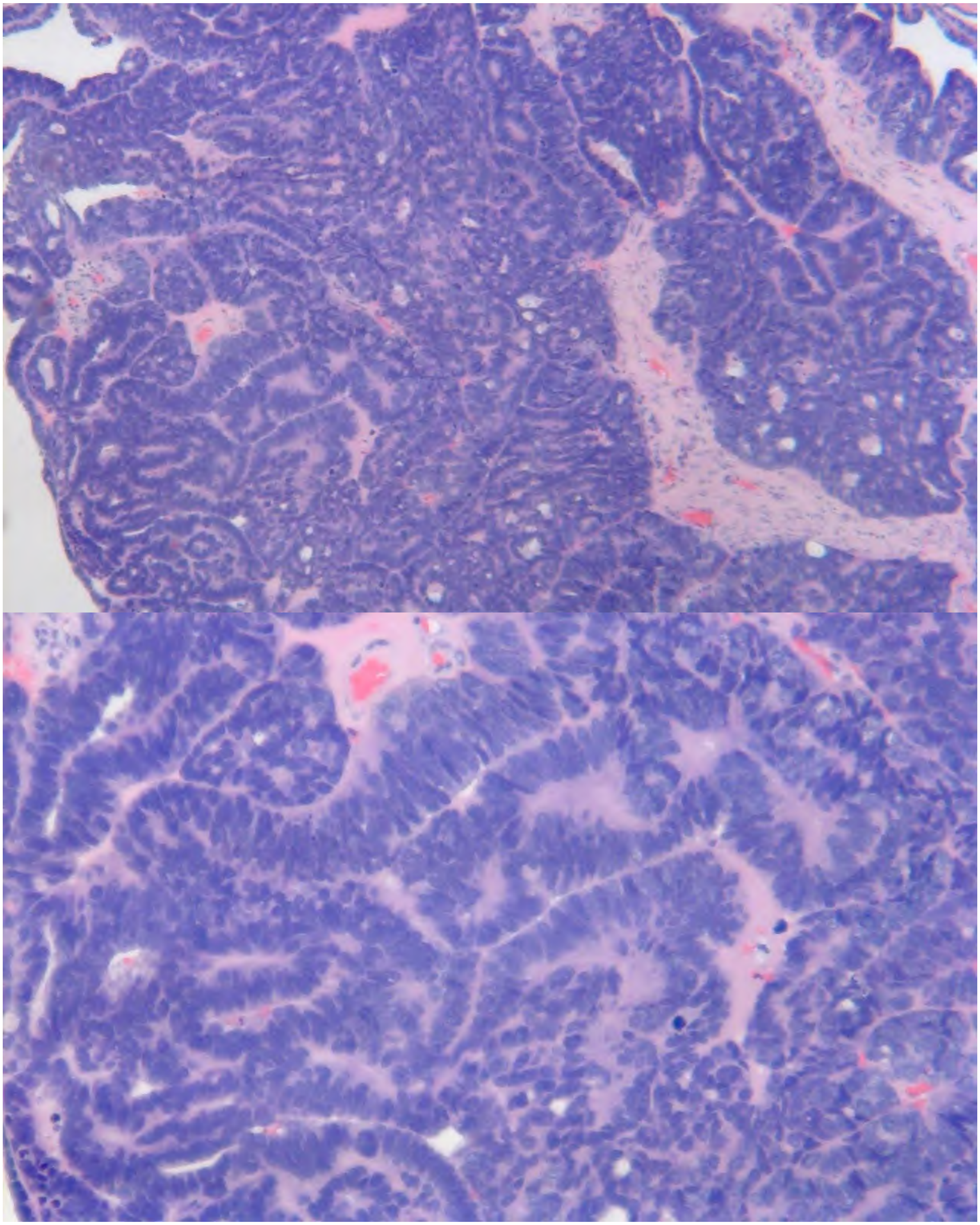

Figure 5. Ovarian endometrioid carcinoma.

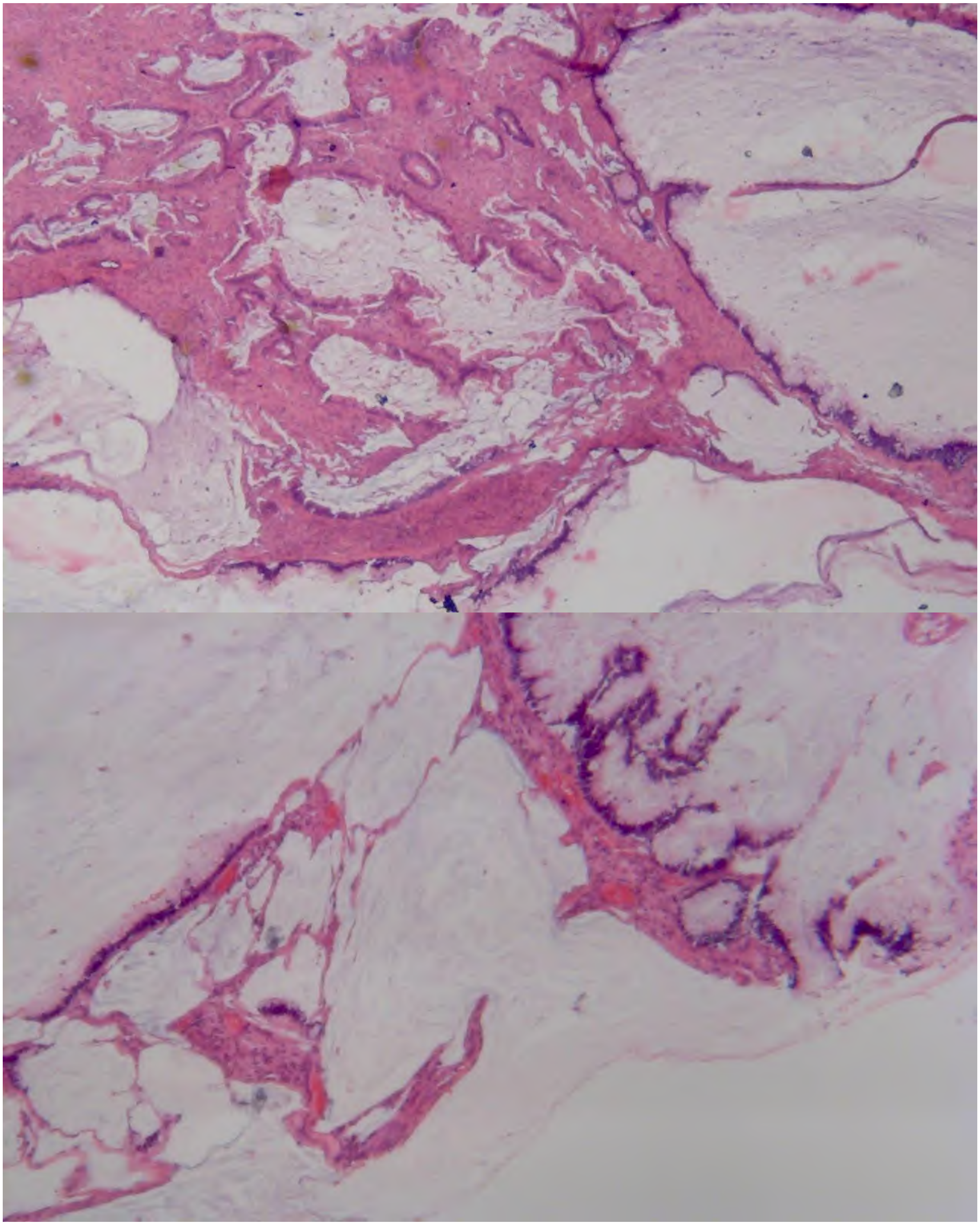

Figure 6. Ovarian mucinous carcinoma.

EXHIBIT A

CURRICULUM VITAE

Date prepared: January 2018

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Topsfield, MA 01983

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Place of Birth: Norwalk, CT

Education:

1995	B.A.	Skidmore College Cum laude
2001	M.D.	The Ohio State University College of Medicine

Postdoctoral Training:

2001-2005	Resident	Pathology, AP/CP	Massachusetts General Hospital
2005-2007	Fellow	Robert E. Scully Fellow Cytopathology, Gynecologic and Perinatal Pathology	Massachusetts General Hospital

Academic Appointments:

2001-2005	Clinical Instructor	Pathology	Harvard Medical School
2005-2007	Graduate Assistant	Pathology	Harvard Medical School
2007-2011	Instructor	Pathology	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions

2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess
2007-2011	Staff Pathologist	Pathology	Beth Israel Deaconess-Needham
2011-Present	Staff Pathologist	Pathology	North Shore Medical Center
2011-Present	Staff Pathologist	Pathology	Newton-Wellesley Hospital
2011-Present	Clinical Affiliate	Pathology	Massachusetts General Hospital

Major Administrative Responsibilities:

2005	Chief Resident, Anatomic Pathology	Massachusetts General Hospital
2007-2011	Course Director, PA501.5 Elective	Harvard Medical School
2010-2011	Associate Director, Cytopathology Fellowship	BIDMC/Harvard
2012-2013	Hematology Laboratory Director NSMC	NSMC/Partners
2013-Present	Autopsy Director, North Shore Medical Center	NSMC/Partners

Major Committee Assignments:

2005-2007	Cytopathology	Junior Member	College of American Pathologists
2005	Path Residency Training Committee	Member	Massachusetts General Hospital
2005	Anatomic Path Quality Assurance	Member	Massachusetts General Hospital
2005	Anatomic Path Steering Committee	Member	Massachusetts General Hospital
2008-2011	Path Resident Selection Committee	Member	Beth Israel Deaconess
2009-2011	Path Residency Planning Committee	Member	Beth Israel Deaconess
2010	Pathology Scheduling Committee	Member	Beth Israel Deaconess
2010-2011	Anatomic Path Quality Assurance	Member	Beth Israel Deaconess

Professional Societies:

1997 – 2001	American Medical Student Association	Member
2001 – Present	Massachusetts Medical Society	Member
2003 – Present	United States and Canadian Academy of Pathology	Member
2005 - Present	College of American Pathologists	Member

Awards and Honors:

1994	Charlotte W. Fahey Prize in Chemistry, Skidmore College
1994	Skidmore College Periclean Honor Society
1995	Phi Beta Kappa, Skidmore College
1995	Cum Laude with Department Honors, Skidmore College
2000	Honors in Pediatric Hematology and Oncology 4th Year Clerkship
2000	Letter of Commendation, Surgery Third Year Clerkship
2000	Letter of Commendation, Neurology Third Year Clerkship
2001	Honors in Anatomic and Clinical Pathology Fourth Year Elective
2001	Honors in Individual Studies in Pathology Fourth Year Elective
2016	Partners in Excellence Team Award

Teaching of Students:

Harvard Medical School Courses:

2007-2009	Respiratory Pathophysiology	
2nd Year Medical Students	Lab Instructor	Three 2 hour sessions, one week

2007-2009 Cardiovascular Pathophysiology
2nd Year Medical Students Lab Instructor Three 2 hour sessions, one week

2007-2011 Core Surgery Clerkship
3rd Year Medical Students Pathology Coordinator One hour lecture/3 months

2009-2011 Principal Clinical Experience
3rd Year Medical Students Mentor Two hour session per week

2009-2011 Principal Clinical Experience – Pathology Elective
3rd Year Medical Students Mentor Minimum 2 hour session/month

Formal Teaching of Residents:

2007 Respiratory Cytology
All pathology residents Beth Israel Deaconess One hour lecture

2007-2011 Respiratory Cytology Quarterly 1 hr microscope session
Pathology residents rotating through Cytology

2008-2011 Fine Needle Aspiration Techniques
All pathology residents Beth Israel Deaconess One hour lecture

2008-2011 Histologic and Cytologic Correlation of Cervical Lesions
All pathology residents Beth Israel Deaconess One hour lecture

Clinical Supervisory and Training Responsibilities:

2007-2011 Core Surgery Clerkship, Pathology Elective BIDMC 2 students/month

Local Invited Presentations:

2005 Cytology/Histology Correlation Clinical Pathology Technician Lecture Series
Department of Pathology, Massachusetts General Hospital

2008 Respiratory Cytology Cytopathology Lecture Series
Department of Pathology, Brigham and Women's Hospital

Current Licensure and Certification:

2005 Full License, Massachusetts

2008 Board certified, Anatomic and Clinical Pathology

2008 Board certified, Cytopathology

Practice Activities:

Surgical Pathology, Cytopathology, Autopsy	North Shore Medical Center
Surgical Pathology, Cytopathology	MGH Ambulatory Care Center
Cytopathology	Massachusetts General Hospital
Clinical Pathology	Newton-Wellesley Hospital

Peer-Reviewed Publications:

Narasimhan V, Malboueuf B, **Hodil SE**. Temperature Induced Interstrand Crosslinks in Cisplatin-DNA Adducts Detected by Electrophoresis and UV Spectrophotometer. *Biochem Mol Biol Int*. 1995;37:843-851.

Grundy FJ, Hodil SE, **Rollins SM**, Henkin TM. Specificity of tRNA-mRNA Interactions in *Bacillus subtilis* tyrS antitermination. *J Bacteriol*. 1997;179:2587-2594.

Rollins S, Prayson RA, McMahon JT, Cohen BH. Diagnostic Yield of Muscle Biopsy in Patients with Clinical Evidence of Mitochondrial Cytopathy. *Am J Clin Pathol*. 2001;116:326-330.

Rollins SE, Rollins SM, Ryan ET. Yersinia Pestis and the Plague. *Am J Clin Pathol*. 2003:119 Suppl:S78-85.

Rollins SE, Young RH, Bell DA. Autoimplants in Serous Borderline Tumors of the Ovary: A Clinicopathologic Study of 30 Cases of a Process to be Distinguished from Serous Adenocarcinoma. *Am J Surg Pathol.* 2006;30:457-462.

Chan MP, Hecht JL, **Kane SE**. Clinicopathologic Correlation of Fetal Vessel Thrombosis in Mono- and Dichorionic Twin Placentas. *J Perinatol*. 2010 Oct; 30(10):660-4.

Kane SE, Hecht JL. Endometrial Intraepithelial Neoplasia Terminology in Practice: 4-Year Experience at a Single Institution. *Int J Gynecol Cancer*. 2012 Mar;31(2):160-165.

Haspel RA, Bhargava P, Gilmore H, **Kane SE**, Powers A, Sepehr A, Weinstein A, Schwartzstein R, Roberts D. Successful Implementation of a Longitudinal, Intergrated Pathology Curriculum During the Third Year of Medical School. *Arch Pathol Lab Med*. 2012 Nov;136(11):1430-6.

Proceedings of Meetings (Poster Presentations):

Rollins S, Prayson RA, McMahon JT, Cohen BH. Diagnostic Yield of Muscle Biopsy in Patients With Clinical Evidence of Mitochondrial Cytopathy. 90th United States and Canadian Academy of Pathology. March 2001. Atlanta, GA.

Rollins SE, Nielsen GP, Hedley-Whyte ET. Light Microscopy, Electron Microscopy, and Mitochondrial Enzyme Function in Muscle Biopsies for Suspected Mitochondrial Cytopathies. 92nd United States and Canadian Academy of Pathology. March 2003. Washington, DC.

Rollins SE, Nielsen GP, Hedley-Whyte ET. Light Microscopy, Electron Microscopy, and Mitochondrial Enzyme Function in Muscle Biopsies for Suspected Mitochondrial Cytopathies. Massachusetts General Hospital Clinical Research Day. June 2003. Boston, MA.

Rollins SE, Young RH, Bell DA. Autoimplants Involving Serous Borderline Tumors of the Ovary: A Clinicopathologic Study of 30 Cases. 93rd United States and Canadian Academy of Pathology. March 2004. Vancouver, BC.

Michaels PJ, **Rollins SE**, Bounds BC, Brugge WR, Pitman MB. Cyst Fluid Analysis and Endoscopic Features Aid in the Preoperative Grading of Intraductal Papillary Mucinous Neoplasms of the Pancreas. 95th United States and Canadian Academy of Pathology. February 2006. Atlanta, GA.

Rollins SE, Clement PB, Young RH. Uterine Tumors Resembling Ovarian Sex Cord Tumors Frequently Have Incorporated Mature Smooth Muscle Imparting a Pseudoinfiltrative Appearance. 96th United States and Canadian Academy of Pathology, March 2007. San Diego, CA.

White SR, Hecht J, **Kane SE**, Fu Y, Cohen DW, Wang HH. Bile duct brush cytology: indeterminate diagnosis is essential. Arch Pathol Lab Med 2009;133:1689.

EXHIBIT B

SARAH E. KANE, M.D.

Board Certified in Anatomic and Clinical Pathology, and Cytopathology

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REFERENCES CITED
AND OTHER MATERIAL AND DATA CONSIDERED

LITERATURE:

1. Acheson ED, Gardner MJ, Pippard EC, and Grime LP. Mortality of two groups of women who manufactured gas masks from chrysotile and crocodilite asbestos: a 40 year follow-up. *Br J Indust Med* 1982;39-344-8.
2. Allaire GS, Goodman ZD, Ishak KG, et al. Talc in liver tissue of intravenous drug abusers with chronic hepatitis. A comparative study. *Am J Clin Pathol* 1989 Nov;92(5):583-8.
3. Antonangelo L, Vargas FS, Teixeira LR, et al. Pleurodesis induced by talc or silver nitrate: Evaluation of collagen and elastic fibers in pleural remodeling. *Lung* 2006;184:105-11.
4. Antony VB, Nasreen N, Mohammed KA, et al. Talc pleurodesis: Basic fibroblast growth factor mediates pleural fibrosis. *Chest* 2004;126:1522-8.
5. Arellano-Orden E, Romero-Falcon A, Juan JM, et al. Small particle-size talc is associated with poor outcome and increased inflammation in thoracoscopic pleurodesis. *Respiration* 2013;86(3):201-9.
6. Aust AE and Eveleigh JF. Mechanisms of DNA oxidation. *Proc Soc Exp Biol Med* 1999;222:246-52.
7. Baandrup L, Faber MT, Christensen J, et al. Nonsteroidal anti-inflammatory drugs and risk of ovarian cancer: systematic review and meta-analysis of observational studies. *Acta Obstet Gynecol Scand* 2013;92(3):245-55.
8. Belotte J, Fletcher NM, Saed MG, et al. A Single Nucleotide Polymorphism in Catalase Is Strongly Associated with Ovarian Cancer Survival. *PLoS One* 2015; 10(8): e0135739.
9. Berge W, Mundt K, Luu H, et al. Genital use of talc and risk of ovarian cancer: a meta-analysis. *Eur J Cancer Prev* 2018 May;27(3):248-257.
10. Berry G, Newhouse ML, Wagner JC. Mortality from all cancers of asbestos factory workers in east London 1933–80. *Occup Environ Med* 2000;57:782–785.
11. Bertolotti M, Ferrante D, Mirabelli D. [Mortality in the cohort of the asbestos cement workers in the Eternit plant in Casale Monferrato (Italy)]. *Epidemiol Prev* 2008;32(4-5):218-28.
12. Blettner M, Sauerbrel W, Schlehofer B, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999 Feb;28(1):1-9.
13. Blount, A. M. Amphibole content of cosmetic and pharmaceutical talcs. *Environ. Health Perspect* 1991; 94:225-230.
14. Booth M, Beral V, and Smith P. Risk factors for ovarian cancer: A case-control study. *Br J Cancer* 1989;60:592-8.
15. Brinton LA, Gridley G, Persson I, et al. Cancer risk after a hospital discharge diagnosis of endometriosis. *Am J Obstet Gynecol* 1997;176:572-9.
16. Brinton LA, Lamb EJ, Moghissi KS, et al. Ovarian cancer risk associated with varying causes of infertility. *Fertil Steril* 2004;82:405-14.
17. Burki T. Asbestos production increases despite WHO opposition. *Lancet Oncol* 2009;10(9):846.

18. Buz'Zard AR and Lau BH. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. *Phytother Res* 2007;21:579-86.
19. Camargo MC, Stayner LT, Straif K, et al. Occupational exposure to asbestos and ovarian cancer: a meta-analysis. *Environ Health Perspect* 2011;119(9):1211-7.
20. Campion A, Smith KJ, Fedulov AV, et al. Identification of foreign particles in human tissues using Raman microscopy. *Anal Chem* 2018 Jul 17;90(14):8362-8369.
21. Centers for Disease Control and Prevention. Principles of epidemiology in public health practice, third edition. An introduction to applied epidemiology and biostatistics. https://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson3/section5.html. Last accessed 11/9/2018.
22. Chang S and Risch HA. Perineal talc exposure and risk of ovarian carcinoma. *Cancer* 1997;79:2396-401.
23. Chen Y, Wu PC, Lang JH, et al. Risk factors for epithelial ovarian cancer in Beijing, China. *Int J Epidemiol* 1992;21:23-9.
24. Cheng DS, Rogers J, Wheeler A, et al. The effects of intrapleural polyclonal anti-tumor necrosis factor alpha (TNF alpha) Fab fragments on pleurodesis in rabbits. *Lung* 2000;178(1):19-29.
25. Churg A. *Pathology of Occupational Disease*. Baltimore: Williams and Wilkins; 1998. Neoplastic asbestos-induced disease; 339–392p.
26. Circu ML, Aw TY. Glutathione and modulation of cell apoptosis. *Biochim Biophys Acta* 2012 Oct;1823(10):1767-77.
27. Clendenen TV, Lundin E, Zeleniuch-Jacquotte A, et al. Circulating inflammation markers and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2011;20(5):799-810.
28. Clin B, Morlais F, Dubois B, Guizard AV, Desoubeaux N, Marquignon MF. Occupational asbestos exposure and digestive cancers—a cohort study. *Aliment Pharmacol Ther* 2009;30:364–374.
29. Cohn LD, Becker BJ. How meta-analysis increases statistical power. *Psychol Methods* 2003 Sep;8(3):243-53.
30. Cook LS, Kamb ML, and Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997;145:459-65.
31. Coughlin SS, Hall IJ. Glutathione S-transferase polymorphisms and risk of ovarian cancer: a HuGE review. *Genet Med* 2002 Jul-Aug;4(4):250-7.
32. Cralley LJ, Key MM, Groth DH, et al. Fibrous and mineral content of cosmetic talcum products. *Am Ind Hyg Assoc J* 1968;29(4):350-4.
33. Cramer DW, Liberman RF, Titus-Ernstoff L, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer* 1999;81:351-6.
34. Cramer DW, Titus-Ernstoff L, McKolanis JR, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1125-31.
35. Cramer DW, Vitonis AF, Terry KL, et al. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology* 2016;27:334-46.
36. Cramer DW, Welch WR, Berkowitz RS, and Godleski JJ. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol* 2007;110:498-501.

37. Cramer DW, Welch WR, Scully RE, and Wojciechowski CA. Ovarian cancer and talc. *Cancer* 1982;50:372-6.
38. deKlerk NH, Musk AW, Williams V, et al. Comparison of measures of exposure to asbestos in former crocidolite workers from Wittenoom Gorge, W. Australia. *Am J Ind Med* 1996;30(5):579-87.
39. Dement JM, Brown DP, Okun A. Follow-up study of chrysotile asbestos textile workers: cohort mortality and case-control analyses. *Am J Ind Med* 1994;26(4):431-47.
40. Dong Y, Walsh MD, Cummings MC, et al. Expression of MUC1 and MUC2 mucins in epithelial ovarian tumours. *J Pathol* 1997;183:311-7.
41. Edwards RP, Huang X, Vlad AM. Chronic inflammation in endometriosis and endometriosis-associated ovarian cancer: new roles for the "old" complement pathway. *Oncoimmunology* 2015;4(5).
42. Egli GE, Newton M. The transport of carbon particles in the human female reproductive tract. *Fertil Steril* 1961;12:151-5.
43. Erickson BK, Conner MG, Landen Jr CN. The role of the fallopian tube in the origin of ovarian cancer. *Am J Obstet Gynecol* 2013;209:409-14.
44. Feng H, Ghazizadeh M, Konishi H, Araki T. Expression of MUC1 and MUC2 mucin gene products in human ovarian carcinomas. *Jpn J Clin Oncol* 2002;32:525-9.
45. Ferrante D, Bertolotti M, Todesco A, et al. Cancer mortality and incidence of mesothelioma in a cohort of wives of asbestos workers in Casale Monferrato, Italy. *Environ Health Perspect* 2007;115(10):1401-5.
46. Fletcher NM, Memaj I, Saed NM. Talcum powder enhances oxidative stress in ovarian cancer. *Reprod Sci Suppl* 2018 March;2154-5A.
47. Fletcher NM, Belotte J, Saed MG, et al. Specific point mutations in key redox enzymes are associated with chemoresistance in epithelial ovarian cancer. *Free Radic Biol Med* 2017 Jan;102:122-132.
48. Folkins, Ann K., Elke A. Jarboe, Jonathan L. Hecht, Michael G. Muto, and Christopher P. Crum. 2018. "Chapter 24 - Assessing Pelvic Epithelial Cancer Risk and Intercepting Early Malignancy." In Diagnostic Gynecologic and Obstetric Pathology (Third Edition), 844–64. Philadelphia: Content Repository Only! https://doi.org/10.1016/B978-0-323-44732-4.00024-8.
49. Frank C LJ. An uncommon hazard: pulmonary talcosis as a result of recurrent aspiration of baby powder. *Respiratory Med CME* 2011;4:109-111.
50. Gardner MJ, Winter PD, Pannett B, Powell CA. Follow up study of workers manufacturing chrysotile asbestos cement products. *Br J Ind Med* 1986;43:726–732.
51. Gates MA, Tworoger SS, Terry KL, et al. Talc use, variants of the GSTM1, GSTT1, and NAT2 genes, and risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:2436-44.
52. Gates MA, Rosner BA, Hecht JL, et al. Risk factors for epithelial ovarian cancer by histologic subtype. *Am J Epidemiol* 2010;171:45-53.
53. Genofre EH, Marchi E, Vargas FS. Inflammation and clinical repercussions of pleurodesis induced by intrapleural talc administration. *Clinics (Sao Paulo)* 2007 Oct;62(5):627-34
54. Genofre EH, Vargas FS, Acencio MM, et al. Talc pleurodesis: evidence of systemic inflammatory response to small size talc particles. *Respir Med* 2009;103(1):91-7.
55. Germani D, Belli S, Bruno C, et al. Cohort mortality study of women compensated for asbestosis in Italy. *Am J Ind Med 1999*;36(1):129-34.

56. Gertig DM, Hunter DJ, Cramer DW, et al. Prospective study of talc use and ovarian cancer. *J Natl Cancer Inst* 2000;92:249-52.
57. Ghio AJ, Taylor DE, Stonehuerner JG, Piantadosi CA, et al. The release of iron from different asbestos structures by hydrogen peroxide with concomitant O2 generation. *Biometals* 1998;11(1):41-7.
58. Godard B, Foulkes WD, Provencher D, et al. Risk factors for familial and sporadic ovarian cancer among French Canadians: a case-control study. *Am J Obstet Gynecol* 1998;179(2):403-10.
59. Gonzalez NL, O'Brien KM, D'Alosisio AA, et al. Douching, Talc Use, and Risk of Ovarian Cancer. *Epidemiology* 2016;27:797-802.
60. Goode EL, Fridley BL, Vierkant RA, et al. Candidate gene analysis using imputed genotypes: cell cycle single-nucleotide polymorphisms and ovarian cancer risk. *Cancer Epidemiol Biomarkers Prev* 2009 Mar;18(3):935-44
61. Goodman MT, Lurie G, Thompson PJ, et al. Association of two common single-nucleotide polymorphisms in the *CYP19A1* locus and ovarian cancer risk. *Endocr Relat Cancer* 2008 Dec;15(4):1055-1060.
62. Graham J and Graham R. Ovarian cancer and asbestos. *Environ Res* 1967;1:115-28.
63. Green A, Purdie D, Bain C, et al. Tubal sterilization, hysterectomy and decreased risk of ovarian cancer. Survey of Women's Health Study Group. *Int J Cancer* 1997;71:948-51.
64. Gross AJ and Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *J Expo Anal Environ Epidemiol* 1995;5:181-95.
65. Gulumian M. The role of oxidative stress in diseases caused by mineral dusts and fibres: current status and future of prophylaxis and treatment. *Mol Cell Biochem* 1999;196(1-2):69-77.
66. Gupta M, Babic A, Beck AH, et al. TNF-α expression, risk factors, and inflammatory exposures in ovarian cancer: evidence for an inflammatory pathway of ovarian carcinogenesis? *Hum Pathol* 2016;54:82-91.
67. Hagemann T, Wilson J, Burke F, et al. Ovarian cancer cells polarize macrophages toward a tumor-associated phenotype. *J Immunol* 2006;176(8):5023-32.
68. Harding AH, Darnton A, Wegerdt J, McElvenny D. Mortality among British asbestos workers undergoing regular medical examinations (1971–2005). *Occup Environ Med* 2009;66:487–495.
69. Harlow BL, Cramer DW, Bell DA, and Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992;80:19-26.
70. Harlow BL and Weiss NS. A case-control study of borderline ovarian tumors: The influence of perineal exposure to talc. *Am J Epidemiol* 1989;130:390-4.
71. Hartge P, Hoover R, Lesher LP, et al. Talc and ovarian cancer. *JAMA* 1983;250(14):1844.
72. Hein MJ, Stayner LT, Lehman E, Dement JM. Follow-up study of chrysotile textile workers: cohort mortality and exposure–response. *Occup Environ Med* 2007;64:616–625.
73. Heller DS, Westhoff C, Gordon RE, and Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996;174:1507-10.
74. Henderson WJ, Joslin CA, Turnbull AC and Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw* 1971;78:266-72.
75. Henderson WJ, Hamilton TC, and Griffiths K. Talc in normal and malignant ovarian tissue. *Lancet* 1979;1:499.

76. Hill AB. The environment and disease: Association or causation? *Proc R Soc Med* 1965;58:295-300.
77. Ho SB, Niehans GA, Lyftogt C, et al. Heterogeneity of mucin gene expression in normal and neoplastic tissues. *Cancer Res* 1993;53:641-51.
78. Hobson J, Wright JL, Churg A. Active oxygen species mediate asbestos fiber uptake by tracheal epithelial cells. *FASEB J* 1990;4(13):3135-9.
79. Houghton SC, Reeves KW, Hankinson SE, et al. Perineal powder use and risk of ovarian cancer. *J Natl Cancer Inst* 2014;106:1-6.
80. Huncharek M, Geschwind JF, and Kupelnick B. Perineal application of cosmetic talc and risk of invasive epithelial ovarian cancer: A meta-analysis of 11,933 subjects from sixteen observational studies. *Anticancer Res* 2003;23:1955-60.
81. Huncharek MS, Muscat JE, Onitilo A, and Kupelnick B. Use of cosmetic talc on contraceptive diaphragms and risk of ovarian cancer: A meta-analysis of nine observational studies. *Eur J Cancer Prev* 2007;16:422-9.
82. Institute of Medicine. *Asebstos: selected cancers.* Washington (DC): National Academies Press (US); 2006.
83. IARC. International Agency for Research on Cancer Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica and Some Silicates IARC Monographs. 1987
84. International Agency for Research on Cancer. Arsenic, metals, fibres, and dusts. *IARC Monogr Eval Carcinog Risks Hum* 2010;100c:219-309.
85. International Agency for Research on Cancer. Arsenic, Metals, Fibres and Dusts. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100C *IARC Monogr Eval Carcinog Risks Hum* Lyon (FR): International Agency for Research on Cancer; 2012.
86. Ishikawa T, Ali-Osman F. Glutathione-associated cis-diamminedichloroplatinum(II) metabolism and ATP-dependent efflux from leukemia cells. Molecular characterization of glutathione-platinum complex and its biological significance. *J Biol Chem* 1993 Sep 25;268(27):20116-25.
87. Jiang Z, Fletcher NM, Ali-Fehmi R, et al. Modulation of redox signaling promotes apoptosis in epithelial ovarian cancer cells. *Gynecol Oncol* 2011 Aug;122(2):418-23.
88. Kindelberger DW, Lee Y, Miron A, et al. Intraepithelial carcinoma of the fimbria and pelvic serous carcinoma: Evidence for a causal relationship. *Am J Surg Pathol* 2007;31:161-9.
89. Klaunig JE, Kamendulis LM, Hocevar BA. Oxidative stress and oxidative damage in carcinogenesis. *Toxicol Pathol* 2010 Jan;38(1):96-109
90. Kobayashi H, Sumimoto K, Moniwa N, et al. Risk of developing ovarian cancer among women with ovarian endometrioma: A cohort study in Shizuoka, Japan. *Int J Gynecol Cancer* 2007;17:37-43.
91. Kotera Y, Fontenot JD, Pecher G, et al. Humoral immunity against a tandem repeat epitope of human mucin MUC1 in sera from breast, pancreatic, and colon cancer patients. *Cancer Res* 1994;54:2856-60.
92. Kurman RJ and Shih IM. The origin and pathogenesis of epithelial ovarian cancer: A proposed unifying theory. *Am J Surg Pathol* 2010;34:433-43.
93. Kurta ML, Moysich KB, Weissfeld JL, et al. Use of fertility drugs and risk of ovarian cancer: results from a U.S.-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2012;21(8):1282-92.

94. Langseth H, Andersen A. Cancer incidence among women in the Norwegian pulp and paper industry. *Am J Ind Med* 1999;36(1):108-13.
95. Langseth H, Hankinson SE, Siemiatycki J, Weiderpass E. Perineal use of talc and risk of ovarian cancer. *J Epidemiol Community Health* 2008;62;358-60.
96. Langseth H, Johansen BV, Nesland JM, et al. Asbestos fibers in ovarian tissue from Norwegian pulp and paper workers. *Int J Gynecol Cancer* 2007;17(1):44-9.
97. Langseth H and Kjaerheim K. Ovarian cancer and occupational exposure among pulp and paper employees in Norway. *Scand J Work Environ Health* 2004;30(5):356-61.
98. Laury AR, Hornick JL, Perets R, et al. PAX8 reliably distinguishes ovarian serous tumors from malignant mesothelioma. *Am J Surg Pathol* 2010;34(5):627-35.
99. Lei XG, Zhu JH, Cheng WH, et al. Paradoxical Roles of Antioxidant Enzymes: Basic Mechanisms and Health Implications. *Physiol Rev* 2016 Jan;96(1):307-64.
100. Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol* 2010 Sep;177(3):1053-64.
101. Lin HW, Tu YY, Lin SY, et al. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol* 2011;12(9):900-4.
102. Lo-Ciganic WH, Zgibor JC, Bunker CH, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drugs, or acetaminophen and risk of ovarian cancer. *Epidemiology* 2012 Mar;23(2):311-9.
103. Longo DL, Young RC. Talc and ovarian cancer. *Lancet* 1979;2(8138):349-51.
104. Loomis D, Dement JM, Wolf SH, Richardson DB. Lung cancer mortality and fibre exposures among North Carolina asbestos textile workers. *Occup Environ Med* 2009;66:535–542.
105. Lundin E, Dossus L, Clendenen T, et al. C-reactive protein and ovarian cancer: a prospective study nested in three cohorts (Sweden, USA, Italy). *Cancer Causes Control* 2009 Sep;20(7):1151-9.
106. Magnani C, Ferrante D, Barone-Adesi F, et al. Cancer risk after cessation of asbestos exposure: a cohort study of Italian asbestos cement workers. *Occup Environ Med* 2008;65(3):164-70.
107. Mallen, AR, MK Townsend, and SS Tworoger. 2018. "Risk Factors for Ovarian Carcinoma." Hematology/Oncology Clinics of North America. https://doi.org/10.1016/j.hoc.2018.07.002.
108. Malone JM, Saed GM, Diamond MP, et al. The effects of the inhibition of inducible nitric oxide synthase on angiogenesis of epithelial ovarian cancer. *Am J Obstet Gynecol* 2006 Apr;194(4):1110-6; discussion 1116-8.
109. Mamo C, Costa G. Mortality experience in an historical cohort of chrysotile asbestos textile workers. 2004. Available from: http://citeseerx.ist.psu.edu/viewdoc/download ?doi=10.1.1.500.2907&rep=rep1&type=pdf
110. Marchiori E, Lourenco S, Gasparetto TD, Zanetti G, Mano CM, Nobre LF. Pulmonary talcosis: imaging findings. *Lung* 2010;188(2):165-171.
111. McDonald JC, Harris JM, Berry G. Sixty years on: the price of assembling military gas masks in 1940. *Occup Environ Med* 2006;63(12):852-5.
112. McSorley MA, Alberg AJ, Allen DS, et al. C-reactive protein concentrations and subsequent ovarian cancer risk. *Obstet Gynecol* 2007;109(4):933-41.
113. Merritt MA, Green AC, Nagle CM, et al. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer* 2008;122:170-6.

114. Mills PK, Riordan DG, Cress RD, and Young HA. Perineal talc exposure and epithelial ovarian cancer risk in the central valley of California. *Int J Cancer* 2004;112:458-64.
115. Moorman PG, Palmieri RT, Akushevich L, et al. Ovarian cancer risk factors in African-American and white women. *Am J Epidemiol* 2009;170(5):598-606.
116. Mossman BT and Churg A. Mechanisms in the pathogenesis of asbestosis and silicosis. *Am J Respir Crit Care Med* 1998;157(5 Pt 1):1666-80.
117. Mossman BT and Landesman JM. Importance of oxygen free radicals in asbestos-induced injury to airway epithelial cells. *Chest* 1983;83(5 Suppl):50S-51S.
118. Mostafa SA, Bargeron CB, Flower RW, et al. Foreign body granulomas in normal ovaries. *Obstet Gynecol* 1985;66:701-2.
119. Najmunnisa N, Mohammed KA, Brown S, et al. Talc mediates angiostasis in malignant pleural effusions via endostatin induction. *Eur Respir J* 2007;29:761-9.
120. Nasreen N, Hartman DL, Mohammed KA, and Antony VB. Talc-induced expression of C-C and C-X-C chemokines and intercellular adhesion molecule-1 in mesothelial cells. *Am J Respir Crit Care Med* 1998;158:971-8.
121. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst* 1999 Sep 1;91(17):1459-67.
122. Ness RB, Grisso JA, Cottreau C, et al. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology* 2000;11:111-7.
123. Newhouse ML, Berry G, Wagner JC, Turok ME. A study of the mortality of female asbestos workers. *Br J Ind Med* 1972;29:134-41.
124. Newhouse ML, Sullivan KR. A mortality study of workers manufacturing friction materials: 1941–1986. *Br J Ind Med* 1989;46:176–179.
125. NIOSH. https://www.cdc.gov/niosh/docs/81-103/pdfs/81-103.pdf Last accessed 11/15/18
126. Notaridou M, Quaye L, Dafou D, et al. Common alleles in candidate susceptibility genes associated with risk and development of epithelial ovarian cancer. *Int J Cancer* 2011 May 1;128(9):2063-74.
127. Occupational Safety and Health Administration. Asbestos. https://www.osha.gov/SLTC/asbestos/ Last accessed 11/9/2018.
128. Ordonez NG. Value of PAX8, PAX2, claudin-4, and h-caldesmon immunostaining in distinguishing peritoneal epithelioid mesotheliomas from serous carcinomas. *Mod Pathol* 2013;26:553-62.
129. Park, HK, J M Schildkraut, AJ Alberg, EV Bandera, JS Barnholtz-Sloan, M Bondy, S Crankshaw, et al. 2018. “Benign Gynecologic Conditions Are Associated with Ovarian Cancer Risk in African-American Women: A Case–Control Study.” Cancer Causes & Control, September. https://doi.org/10.1007/s10552-018-1082-4.
130. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systemic review and meta-analysis. *Epidemiology* 2018 Jan;29(1):41-49.
131. Piek JM, Verheijen RH, Kenemans P, et al. BRCA1/2-related ovarian cancers are of tubal origin: A hypothesis. *Gynecol Oncol* 2003;90(2):491.
132. Pike MC, Pearce CL, Peters R, et al. Hormonal factors and the risk of invasive ovarian cancer: a population-based case-control study. *Fertil Steril* 2004 Jul;82(1):186-95.
133. Pinheiro SP, Hankinson SE, Tworoger SS, et al. Anti-MUC1 antibodies and ovarian cancer risk: Prospective data from the Nurses’ Health Studies. *Cancer Epidemiol Biomarkers Prev* 2010:19:1595-601.

134. Pira E, Pelucchi C, Palmas A, et al. Cancer mortality in a cohort of asbestos textile workers. *Br J Cancer* 2005;92(3):580-6.
135. Plato N, Martinsen JI, Kjaerheim K, et al. Mesothelioma in Sweden: Dose-response analysis for exposure to 29 potential occupational carcinogenic agents. *Saf Health Work* 2018 Sep;9(3):290-295. doi: 10.1016/j.shaw.2018.04.003. Epub 2018 Apr 21
136. Poole EM, Lee IM, Ridker PM, et al. A prospective study of circulating C-reactive protein, interleukin-6, and tumor necrosis factor α receptor 2 levels and risk of ovarian cancer. *Am J Epidemiol* 2013;178(8):1256-64.
137. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;48(5):646-790.
138. Reid A, Heyworth J, de Klerk N, et al. The mortality of women exposed environmentally and domestically to blue asbestos at Wittenoom, Western Australia. *Occup Environ Med* 2008;65(11):743-9.
139. Reid A, de Klerk N, Musk AW. Does exposure to asbestos cause ovarian cancer? A systematic literature review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2011;20(7):1287-95.
140. Reid A, Segal A, Heyworth JS, et al. Gynecologic and breast cancers in women after exposure to blue asbestos at Wittenoom. *Cancer Epidemiol Biomarkers Prev* 2009;18(1):140-7.
141. Reuter S, Gupta SC, Chaturvedi MM, et al. Oxidative stress, inflammation, and cancer: how are they linked? *Free Radic Biol Med* 2010 Dec 1;49(11):1603-16.
142. Richards JS, Russell DL, Ochsner S, et al. Ovulation: New dimensions and new regulators of the inflammatory-like response. *Annu Rev Physiol* 2002;64:69-92.
143. Risch HA and Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 1995;4:447-51.
144. Robledo R and Mossman B. Cellular and molecular mechanisms of asbestos-induced fibrosis. *J Cell Physiol* 1999;180(2):158-66.
145. Roggli VL, Pratt PC. Numbers of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. *Hum Pathol* 1983 Apr;14(4):355-61.
146. Roggli VL, Pratt PC, Brody AR. Asbestos content of lung tissue in asbestos associated diseases: a study of 110 cases. *Br J Ind Med* 1986 Jan;43(1):18-28.
147. Rojas V, Hirshfield KM, Ganesan S, et al. Molecular Characterization of Epithelial Ovarian Cancer: Implications for Diagnosis and Treatment. *Int J Mol Sci* 2016 Dec 15;17(12). pii: E2113.
148. Rosenblatt KA, Szklo M, and Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol* 1992;45:20-5.
149. Rosenblatt KA, Weiss NS, Cushing-Haugen KL, et al. Genital powder exposure and the risk of epithelial ovarian cancer. *Cancer Causes Control* 2011;22:737-42.
150. Rosler JA, Woitowitz HJ, Lange HJ, et al. Mortality rates in a female cohort following asbestos exposure in Germany. *J Occup Med* 1994;36(8):889-93.
151. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: Analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet* 2012;379:1602-12.
152. Saed GM, Ali-Fehmi R, Jiang ZL, et al. Myeloperoxidase serves as a redox switch that regulates apoptosis in epithelial ovarian cancer. *Gynecol Oncol* 2010 Feb;116(2):276-81.
153. Saed GM, Diamond MP, Fletcher NM. Updates of the role of oxidative stress in the pathogenesis of ovarian cancer. *Gynecol Oncol* 2017;145(3):595-602.

154. Saed GM, Morris RT, Fletcher NM. New insights into the pathogenesis of ovarian cancer: Oxidative stress. *Ovarian Cancer – From Pathogenesis to Treatment.* DOI: 10.5772/intechopen.73860. 2018. 83-110p.
155. Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. *Curr Biol* 2014 May 19;24(10):R453-62.
156. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: The African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol Biomarkers Prev* 2016;25:1411-17.
157. Senthil K, Aranganathan S, Nalini N. Evidence of oxidative stress in the circulation of ovarian cancer patients. *Clin Chim Acta* 2004;339:27–32.
158. Shukla A, MacPherson MB, Hillegass J, et al. Alterations in gene expression in human mesothelial cells correlate with mineral pathogenicity. *Am J Respir Cell Mol Biol* 2009 Jul; 41(1): 114–123.
159. Stanton MF and Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 1972;48(3):797-821.
160. Straif K, Benbrahim-Talloa L, Baan R, et al. Special Report: Policy. A review of human carcinogens–Part C: metals, arsenic, dusts, and fibres. *Lancet Oncol* 2009;10:453–454.
161. Susser M. What is a cause and how do we know one? A grammar for pragmatic epidemiology. *Am J Epidemiol* 1991;133(7):635-48.
162. Suzuki Y, Kohyama N. Translocation of inhaled asbestos fibers from the lung to other tissues. *Am J Ind Med* 1991;19(6):701-704.
163. Szeszenia-Dabrowska N, Urszula W, Szymczak W, Strzelecka A. Mortality study of workers compensated for asbestosis in Poland, 1970–1997. *Int J Occup Med Environ Health* 2002;15:267–78.
164. Terry KL, Karageorgi S, Shvetsov YR, et al. Genital powder use and risk of ovarian cancer: A pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res* 2013;6:811-21.
165. Terry KL, Titus-Ernstoff L, McKolanis JR, et al. Incessant ovulation, mucin 1 immunity, and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev* 2007;16:30-5.
166. Toriola AT, Grankvist K, Aqborsanqaya CB, et al. Changes in pre-diagnostic serum C-reactive protein concentrations and ovarian cancer risk: a longitudinal study. *Ann Oncol* 2011;22(8):1916-21.
167. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin* 2018 Jul;68(4):284-296.
168. Trabert B, Ness RB, Wei-Hsuan LC, et al. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: A pooled analysis in the ovarian cancer association consortium. *J Natl Cancer Inst* 2014;106:1-11.
169. Tzonou A, Polychronopoulou A, Hsieh CC, et al. Hair dyes, analgesics, tranquilizers and perineal talc application as risk factors for ovarian cancer. *Int J Cancer* 1993;55(3):408-10.
170. Upadhyay D and Kamp DW. Asbestos-induced pulmonary toxicity: role of DNA damage and apoptosis. *Exp Biol Med (Maywood)* 2003;228(6):650-9.
171. van den Heuvel MM, Smit HJ, Barbierato SB, et al. Talc-induced inflammation in the pleural cavity. *Eur Respir J* 1998;12:1419-23.
172. Vasama-Neovonen K, Pukkala E, Paakkulainen H, et al. Ovarian cancer and occupational exposures in Finland. *Am J Ind Med* 1999;36(1):83-9.
173. Venter PF, Iturralde M. Migration of a particulate radioactive tracer from the vagina to the peritoneal cavities and ovaries. *Afr Med J* 1979;55:917-9.

174. Vlad AM, Diaconu I, Gantt KR. MUC1 in endometriosis and ovarian cancer. *Immunol Res* 2006;36(1-3):229-36.
175. Waris G, Ahsan H. Reactive oxygen species: role in the development of cancer and various chronic conditions. *J Carcinog* 2006;5:14.
176. Wasserstein RL, Lazar NA. The ASA's statement on p -values: Context, process, and purpose. *Am Stat* 2016;70:2: 129-133, DOI:10.1080/00031305.2016.1154108
177. Whittemore AS, Wu ML, Paffenbarger RS, et al. Personal and environmental characteristics related to epithelial ovarian cancer. II. Exposures to talcum powder, tobacco, alcohol, and coffee. *Am J Epidemiol* 1988;128:1228-40.
178. Wignall BK and Fox AJ. Mortality of female gas mask assemblers. *Br J Indust Med* 1982;39-34-8.
179. Wilcsynska U, Szymaczak W, Szeszenia-Dabrowska N. Mortality from malignant neoplasms among workers of an asbestos processing plant in Poland: results of prolonged observation. *Int J Occup Med Environ Health* 2005;18(4):313-26.
180. Wong C, Hempling RE, Piver MS, et al. Perineal talc exposure and subsequent epithelial ovarian cancer: a case-control study. *Obstet Gynecol* 1999;93:372-6.
181. Wu AH, Pearce C, Tseng CC, et al. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer* 2009;124:1409-15.
182. Wu AH, Pearce CL, Tseng CC, et al. African Americans and Hispanics remain at lower risk of ovarian cancer than non-Hispanic Whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol Biomarkers Prev* 2015 Jul;24(7):1094-100.
183. Wyroba E, Suski S, Miller K, et al. Biomedical and agricultural applications of energy dispersive X-ray spectroscopy in electron microscopy. *Cell Mol Biol Lett* 2015 Sep;20(3):488-509.
184. Xie C, Reusse A, Dai J, et al. TNF-alpha increases tracheal epithelial asbestos and fiberglass binding via a NF-kappaB-dependent mechanism. *Am J Physiol Lung Cell Mol Physiol* 2000;279(3):L608-14.
185. Yan B, Wang H, Rabbani ZN, et al. Tumor necrosis factor-alpha is a potent endogenous mutagen that promotes cellular transformation. *Cancer Res* 2006;66(24):11565-70.
186. Zhou Z, Zeng F, Yuan J, et al. Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis. *Cancer Causes Control* 2017;28(5):415-428.

OTHER SOURCES:
1. Birrer, Michael. Expert Report of Michael Birrer, MD, PhD. 5/4/17.
2. Deposition of Alice Blount, Ingham v. Johnson & Johnson, et al. (Cir. Ct. of the City of St. Louis, MO) (April 13, 2018).
3. Chodosh, Lewis A. Opinions of Lewis A. Chodosh, MD, PhD. 10/16/15.
4. Chodosh, Lewis A. Trial testimony in Brandi Carl and Joel Carl, Diana Balderrama and Gilbert Balderrama, v. Johnson & Johnson, Imerys Talc America, et al; Atlantic County Courthouse Cases ATL-L-6546-14 and ATL-L-2648-15. 8/19/16.
5. Cohen, Samuel M. Cosmetic talc and the development of ovarian cancer. 10/15/15.
6. Cramer, Daniel W. Opinion on the relationship between ovarian cancer and cosmetic talc use: Causality and relevance to the case of Ms. Deane Berg (Civil Action Number 4:09-CV-04179-KES). 8/24/11.
7. Cramer, Daniel W. Opinion on the relationship between ovarian cancer and cosmetic talc use: Causality and relevance to the case of Jaqueline Fox (Civil Action Number 1422-CC09012). 7/31/15.
8. Expert Report of Michael Crowley, PhD, In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (Nov. 12, 2018).
9. Godelski, John J. Expert report in the case of Jaqueline Fox. 6/4/15.
10. Deposition & Exhibits of John Hopkins, PhD, In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (Aug. 16 & 17, 2018; Oct. 26, 2018; and Nov. 5, 2018).
11. Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD. Analysis report: MAS Project #14-1683 Johnson's Baby Powder sample set. 4/28/17.
12. Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD. Analysis of Johnson & Johnson Baby Powder and Valiant Shower to Shower products for amphibole (tremolite) asbestos. 8/2/17.
13. Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD. TEM analysis of historical 1978 Johnson's Baby Powder sample for amphibole asbestos. 2/16/18.
14. Expert Report of William E. Longo, PhD and Mark W. Rigler, PhD, In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (Nov. 14, 2018).
15. Ness, Roberta B. Report on the question of whether genital talc use causes ovarian cancer. 8/15.
16. Deposition & Exhibits of Julie Pier, In re: Talcum Power Prod. Liab. Litig., MDL No. 2738 (Sept. 12 & 13, 2018).
17. Siemiatycki, Jack. Expert report of Jack Siemiatycki, MSc, PhD on talc use and ovarian cancer. 10/4/16.

Exhibit 58

Foreign Body Granulomas in Normal Ovaries

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N. B. ROSENSHEIN, MD, T. H. PARMLEY, MD, AND J. D. WOODRUFF, MD

In 100 consecutive cases in which grossly normal ovaries were removed at the time of pelvic surgery, 9% were found to contain crystalline foreign particles. An additional 9% contained cortical granulomas. In four of six cases, computer-assisted x-ray analysis of the crystalline foreign particles was successful and revealed magnesium and silicon. ***(Obstet Gynecol 66:701, 1985)***

To make plausible the suggestion that inorganic particulate matter plays a role in the development of proliferative disorders in the female pelvis,[1-5] it is necessary to demonstrate that such matter is capable of producing proliferations under some circumstances. It is also necessary to demonstrate that particulate matter is actually present in the female pelvis with sufficient frequency to account for the amount of observed disease. The present study was designed to address this second question; it does not address the first. It also seeks to determine the elemental nature of the particles observed.

Materials and Methods

In 100 consecutive cases in which grossly normal ovaries were removed at the time of pelvic surgery for other indications, the entire gonad(s) was submitted for histologic examination. A total of 175 normal ovaries were examined. Two to five paraffin blocks were made from each excised gonad, and an average of three sections per ovary were studied. Findings in these 175 ovaries were divided into four groups: cases in which there were no histologic abnormalities, group 1; cases in which there were laminated calcifications, classically referred to as "psammoma bodies," group 2 (Figure 1); cases in which there were foci of reticular stroma with or without inflammation that have been classically referred to as "cortical granulomas," but have been described as endometriosis by others,[6] group 3 (Figure 2); and cases in which foci similar to those in group 3 appeared and which additionally contained foreign body type giant cells and associated crystalline foreign body, group 4 (Figure 3). If two ovaries were removed from one patient, they were classified together as a single case.

Figure 1. Two laminated focal calcifications occupy papillary fronds in this proliferating pelvic neoplasm.

Six examples of crystalline foreign bodies were then processed for examination by scanning electron mi-

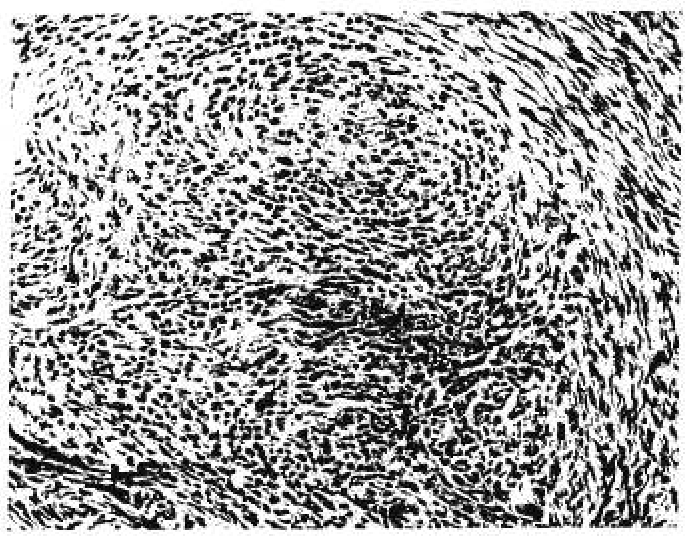

Figure 2. This focus of inflammation was present in the ovarian cortex. Although granulomatous in nature, no giant cells or particulate foreign matter is observed.

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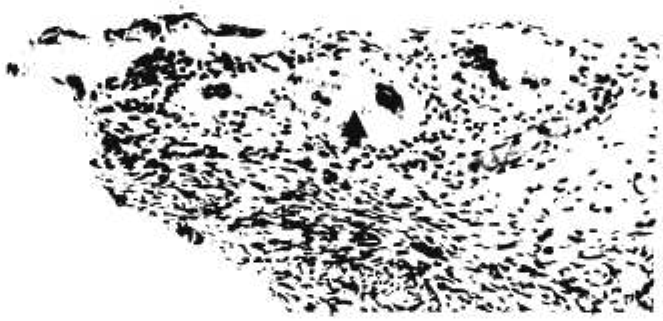

Figure 3. This focus of inflammation in the ovarian cortex contains giant cells. The clefts within the giant cells were filled with refractile crystalline material (*arrows*).

croscopy (ETEC microscope). This consisted of making a number of visible light micrographs in order to record the location of foreign bodies in the specimen and then removing the slide cover slips. The exposed specimens were then mounted on an electron microscope slide and carbon coated. Using appropriate computer-assisted microscopic x-ray analysis, the elemental composition of the crystalline foreign bodies were determined in four cases. In the two other cases, the foreign body was lost when the cover slip was removed.

Results

One hundred seventy-five grossly normal ovaries were removed at the time of pelvic surgery. The surgery was performed for the indications listed in Table 1. Seventy-two cases were classified in group 1 (Table 2).

Computer-assisted x-ray analysis of the crystalline foreign bodies was successful in four of six cases and demonstrated that the particles were composed largely of magnesium and silicon. The mean ages of each

Table 1. Pelvic Surgery for Various Gynecologic Disorders

Diagnosis	No. of cases
Myomata uteri	42
Endometrial carcinoma	18
Cervical carcinoma	10
Endometrial & cervical carcinoma	1
Mixed mesodermal tumor of cervix	1
Uterine leiomyosarcoma	1
Adenomyosis	3
Parovarian cyst	2
Unilateral ovarian neoplasm	5
Endometrial polyp hyperplasia	1
Salpingitis	4
Pelvic endometriosis	3
Chronic pelvic pain	2
Pelvic inflammatory disease	1
Dysfunctional uterine bleeding	6
Total	100

Table 2. Findings in 100 Consecutive Cases in Which a Grossly Normal Gonad(s) Was Removed

Group	No. of cases	Mean age	% Previous laparotomy
1	72	44	36
2	10	50	30
3	9	52	22
4	9	62	44

group and the percentage with a history of laparotomy also are listed in Table 2.

Discussion

The most common compounds containing magnesium silicates in industrial North America are talc and asbestos. As reported,[1–3,5] it is not a new observation that talc may be found in the pelvis, nor are talc granulomas in and of themselves new observations. However, the fact that 9% of the women operated on in the Johns Hopkins Hospital for pelvic disease appeared to have magnesium silicate granulomas in their normal ovaries, and that an additional 9% contained histologic entities that were very similar, represents a higher incidence than the authors had suspected. The exact figure is probably not relevant as it, undoubtedly, varies from population to population, depending on the exposure sustained by that given population. Nevertheless, in at least one geographic area, the incidence of foreign body contamination in the pelvis is sufficiently high to account for the incidence in that geographic locale of proliferative disorders seen at that anatomic site.

References

1. Graham J, Graham R: Ovarian cancer and asbestos. Environ Res 1:115, 1967
2. Henderson WJ, Joslin CAF, Turnbull AC, et al: Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw 78:266, 1971
3. Longo DL, Young RC: Cosmetic talc and ovarian cancer. Lancet ii:349, 1979
4. Parmley TH, Woodruff JD: The ovarian mesothelioma. Am J Obstet Gynecol 120:234, 1974
5. Cramer DW, Welch WR, Scully RE, et al: Ovarian cancer and talc: a case-control study. Cancer 50:372, 1982
6. Hughesdon PE: The endometrial identity of benign stromatosis of the ovary and its relation to other forms of endometriosis. J Pathol 119:201, 1976

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Exhibit 59

Presence of Talc in Pelvic Lymph Nodes of a Woman With Ovarian Cancer and Long-Term Genital Exposure to Cosmetic Talc

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BACKGROUND: Although epidemiologic studies suggest talc use may increase ovarian cancer risk, there is no proof that talc used externally reaches the pelvis.

CASE: A 68-year-old woman with stage III ovarian papillary serous carcinoma revealed she had used talc daily for 30 years to powder her genital area. Examination of her pelvic lymph nodes under polarized light microscopy showed diffuse areas of birefringence compatible with talc, confirmed by scanning electron microscopy and X-ray spectroscopy.

CONCLUSION: This description of talc in pelvic lymph nodes of a woman with ovarian cancer and decades of exposure to talc may prompt new studies and offer new insights into the biologic basis for the consistent, but debated, association between talc use and ovarian cancer.
(Obstet Gynecol 2007;110:498–501)

An epidemiologic association between the use of cosmetic talc in genital hygiene and ovarian cancer was first described in 1982, and many subsequent studies found talc use to increase risk for ovarian cancer.[1] However, the causality of the relationship has been challenged for several reasons.[2] First, the association is a relatively weak one (ie, summary relative risk of approximately 1.3). Second, no clear increase in risk with duration of use has been found in most studies. Third, the ability of talc used in the genital area to enter the pelvic cavity has not been conclusively proven. At the time of pelvic surgery for ovarian cancer, pelvic lymph nodes are commonly sampled for staging purposes, but pathologic examination of the nodes is focused on the presence or absence of metastatic disease. More careful examination of pelvic lymph nodes from women with ovarian cancer may contribute to new perspectives in the debate regarding the role of talc in the causation of ovarian cancer, as illustrated by the following case.

CASE

A 68-year-old, married woman presented with abdominal swelling. A computed tomographic scan revealed a 13-cm pelvic mass, and her serum CA 125 level was more than 1,000. She was referred to the Gynecologic Oncology Service at the Brigham and Women's Hospital, where cytoreductive surgery was performed, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and pelvic lymph node sampling. A stage III papillary serous carcinoma with a minor clear cell component was found. Metastatic serous carcinoma was described in two of six right external iliac and obturator nodes. Postoperatively, the patient was referred for chemotherapy. She also consented to our interview about risk factors for ovarian cancer. This study is approved by the Dana Farber–Harvard Cancer Center Institutional Review Board and permits administration of general and dietary questionnaires, blood donation, and investigation of surgical specimen(s) after written informed consent. The patient's past history included three term deliveries followed by a tubal ligation. She had not smoked, used oral contraceptives, or used postmenopausal hormone therapy other than 6 months of progesterone therapy to regulate periods around the time of menopause, which occurred at age 50. There is a family history of colon cancer in a sister and maternal grandmother. At our interview, the patient stated she had used talc daily for 30 years as a body powder on the perineum and also applied it to underwear and sanitary napkins.

In searching for ideas to help clarify the association between talc use and ovarian cancer, we consulted with an expert on mesothelioma (J.G.), who pointed out that asbestos and other particulate material commonly migrates to lymph nodes.[3,4] We decided that a more systematic examination of pelvic lymph nodes from ovarian cancer cases might be in order, beginning with this case. In examining the patient's pelvic lymph nodes, no distinct particulates were seen under regular light microscopy, although a diffuse histocytic reaction was noted, even in a node without metastases (Fig. 1A). Under polarized light, diffuse

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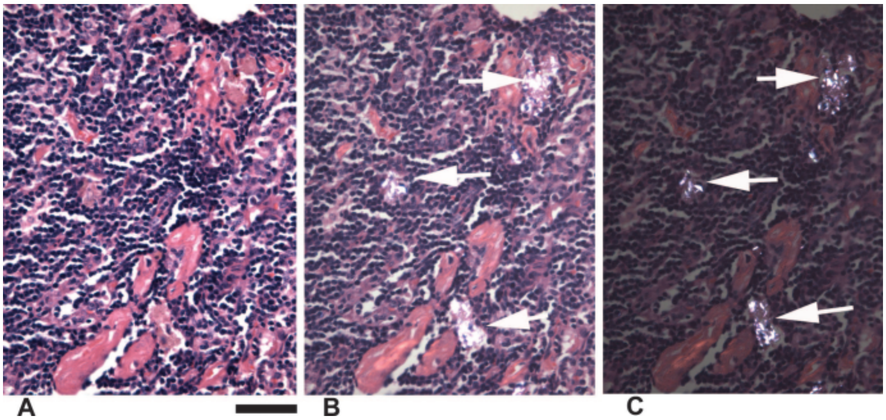

Fig. 1. Hematoxylin and eosin–stained section of a lymph node from the case showing morphologic findings with no polarization of the microscope light and with combinations of polarized and incident light at several different levels. **A.** Nodal morphology is illustrated and reveals no particulates seen without polarized light, but clusters of histiocytes are more prominent than usual. **B.** This panel shows the same field with polarized light plus additional light to view tissue context; birefringence is noted especially in areas of histiocyte clusters. *Arrows* are used to call attention to the birefringent particles. **C.** This shows the same field without added light, revealing the particulate nature of the birefringent material. *Arrows* highlight the particulate. Magnification bar shows 100 μm and applies to all three panels.

Cramer. Talc in Pelvic Lymph Nodes. Obstet Gynecol 2007.

birefringence was seen corresponding to the areas of histiocyte infiltration (Fig. 1B). Figure 1C shows the same field under polarization with no added light, revealing the particulate nature of the material, compatible with talc. Three of this patient's four nodes (not containing metastases) displayed polarizing material. Using methods described by Shelburne et al,[5] we next examined lymph nodes from this patient by combined scanning electron microscopy and energy dispersive X-ray spectroscopy. Scanning electron microscopy revealed plate-like particulates in the 5–10 μm range within the lymph node, in which energy dispersive X-ray spectroscopy showed a magnesium and silicate signature—compatible with talc (Fig. 2A,B). Dystrophic calcium deposits were also found within her nodes, probably a consequence of nodal aging. Of nodes from the next 12 patients examined, this case was strongest for birefringence; but these nodes have not yet been subjected to scanning electron microscopy or energy dispersive X-ray spectroscopy. Figure 3 illustrates a node negative for polarization (or histiocyte reaction) from a patient with ovarian cancer who had not used talc.

COMMENT

Talc is a hydrous magnesium silicate chemically similar to asbestos but structurally quite different. Asbestos has a fiber-like structure and talc a plate-like one. Because of this difference, it has been argued that the relationship between asbestos and mesothelioma should not be invoked to explain how talc might cause ovarian cancer. However, one feature of expo-

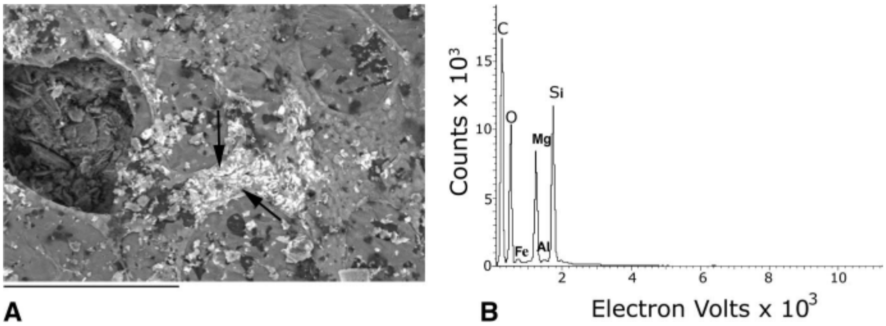

Fig. 2. Analytical microscopy. **A.** Scanning electron microscopy of a histologic section of the lymph node from the case shows a large collection of plate-like particulates in the 5–10 μm range *(arrows)* as well as scattered individual particulates. Magnification bar shows 100 μm. **B.** X-ray spectrum taken from the central bright area with particles reveals a Magnesium (Mg), Silicon (Si), and Oxygen (O) signature compatible with talc. A Carbon (C) signal is coming from the tissue or the underlying Carbon plancette or both.

Cramer. Talc in Pelvic Lymph Nodes. Obstet Gynecol 2007.

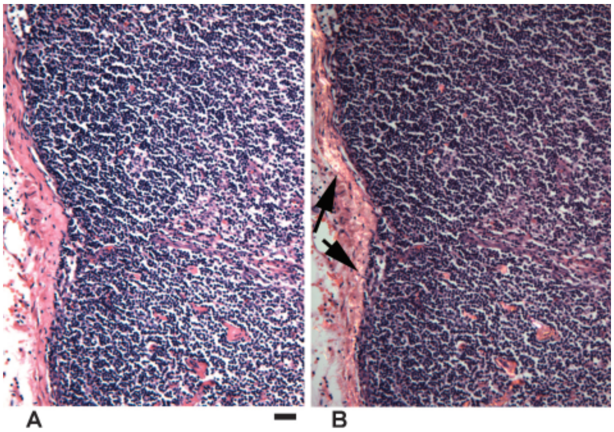

Fig. 3. Comparative node section illustrated from a woman reporting no talc use. **A.** Hematoxylin and eosin stained section showing fewer macrophages than seen in the node in Figure 1A. Magnification bar shows 100 μm. **B.** Polarized light examination of the same area of the node showing only some birefringence in the node capsule *(arrows)* compatible with collagen.

Cramer. Talc in Pelvic Lymph Nodes. Obstet Gynecol 2007.

sure that the minerals do have in common is nodal dissemination. Migration and entrapment in lymph nodes is observed in human asbestos exposure and correlates with the asbestos burden.[3] Talc has also been described in pulmonary lymph nodes of talc miners.[4] However, a MEDLINE search of (all language) publications between January 1950 and February 2007 using the search terms, "talc," "birefringence," "histiocytosis," "lymph nodes," and "ovarian neoplasms," revealed no reports of talc in lymph nodes of ovarian cancer patients.

In one of the few studies in women to evaluate the potential for talc to migrate into the pelvis, Heller et al studied normal ovaries from women having oophorectomy for benign disease.[6] The protocol involved a multistep process of tissue rehydration, blotting, drying, digestion, rehydration, centrifugation, and multiple washes. After this process, polarizing bodies were found in all ovarian specimens examined by light microscopy. By electron microscopy, tissues from 5 of 12 women who regularly used talc and 6 of 12 who had not were found to have particles consistent with talc. The investigators concluded that talc can be found in ovaries but that this does not correlate with genital talc use. Contamination that might have been introduced during extensive processing is a potential weakness of this study.

In this case report, we describe examination of pelvic lymph nodes from a woman with ovarian cancer who had been a long-term talc user. Particles compatible with talc were clearly visible under polarized light in regular hematoxylin and eosin–stained sections from her pelvic nodes, which were then shown by scanning electron microscopy and energy dispersive X-ray spectroscopy to be talc. Thus, as opposed to the aforementioned study, we focused on pelvic lymph nodes rather than ovaries; and talc was shown to be present in macrophages within the actual tissue, ruling out contamination during processing.

In reporting this case, we are not proposing that pelvic lymph nodes from women with ovarian cancer must now be subjected to electron microscopy. However, pathologists may wish to examine pelvic lymph nodes with evidence of histiocytic infiltrates by polarized light microscopy. Clear evidence of polarization may be reported so that clinicians can obtain information about potential talc exposure, if this information has not already been collected. Also we are not claiming that a causal relationship between ovarian cancer and talc use is proven for this case or in general. Because case reports cannot establish causality, we have begun a more extensive study of nodes with two purposes. First it is necessary to establish in a quantitative manner the likelihood of finding talc in lymph nodes of women with ovarian cancer and correlate this by whether they did or did not use talc. Second, studies of immune markers in nodes may help make the case for a causal connection.

What we do hope this case report accomplishes is to infuse a fresh perspective on the talc and ovarian cancer association. Previous biologic arguments linking talc and ovarian cancer have been based upon: similarities between talc and asbestos, the ability of talc to reach the ovaries through the open female tract, and induction of a mesothelioma-like cancer from the ovarian epithelium. Our new perspective would not depend upon structural similarities between talc and asbestos. The adverse effects of talc may relate to its ability to induce an inflammatory reaction, a well-established property of talc, independent of any similarity to asbestos.[7] Also, we don't believe that talc needs to reach the ovaries to affect ovarian cancer risk; rather, the harmful effects of talc may involve inflammatory reactions in the lower genital tract, including the upper vagina, cervix, and endometrium. These tissues express the surface glycoprotein human mucin 1, MUC1, whose function is to protect cells from environmental stressors. It is likely that chronic talc exposure is one factor that upregulates MUC1 expression. Human mucin 1 is related to CA 125 (MUC16), and like CA 125 is overexpressed in ovarian cancer. It is known that women with ovarian cancer who have anti-MUC1 antibodies survive longer, leading us to propose that

many risk factors for ovarian cancer may be explained by their ability to raise or lower MUC1 immunity.[8] Looking at predictors of anti-MUC1 antibodies, talc use was a factor that lowered anti-MUC1 antibodies. Thus, rather than a direct carcinogenic effect on ovarian epithelium, immune dysregulation involving MUC1 may be induced by chronic talc use that may lower protective immunity. Furthermore, sequestration of talc in nodes may affect antigen processing and be another important element in the postulated immune dysregulation.

In conclusion, this description of talc in pelvic lymph nodes of a long-term talc user with ovarian cancer may begin to reshape understanding about the relationship between talc and ovarian cancer and shed new light on whether talc used externally in the genital area is capable of migrating into the pelvis.

REFERENCES

1. Cramer DW, Liberman RF, Titus-Ernstoff L, Welch WR, Greenberg ER, Baron JA, et al. Genital talc exposure and risk of ovarian cancer. Int J Cancer 1999;81:351–6.
2. Wehner AP. Cosmetic talc should not be listed as a carcinogen: comments on NTP's deliberations to list talc as a carcinogen. Regul Toxicol Pharmacol 2002;36:40–50.
3. Friedrichs KH. Electron microscopic analyses of dust from the lungs and the lymph nodes of talc-mine employees. Am Ind Hyg Assoc J 1987;48:626–33.
4. Roggli VL, Benning TL. Asbestos bodies in pulmonary hilar lymph nodes. Mod Pathol 1990;3:513–7.
5. Shelburne JD, Estrada H, Hale M, Ingram P, Tucker JA. Correlative microscopy and microprobe analysis in pathology. In: Bailey GW, editor. Proceedings of the 47th annual meeting of the Microscopy Society of America. Vol 900. San Francisco (CA): San Francisco Press; 1989.
6. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. Am J Obstet Gynecol 1996;174:1507–10.
7. van den Heuvel MM, Smit HJ, Barbierato SB, Havenith CE, Beelen RH, Postmus PE. Talc-induced inflammation in the pleural cavity. Eur Respir J 1998;12:1419–23.
8. Cramer DW, Titus-Ernstoff L, McKolanis JR, Welch WR, Vitonis AF, Berkowitz RS, et al. Conditions associated with antibodies against the tumor-associated antigen MUC1 and their relationship to risk for ovarian cancer. Cancer Epidemiol Biomarkers Prev 2005;14:1125–31.

Postpartum Sudden Death From Pulmonary Hypertension in the Setting of Portal Hypertension

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BACKGROUND: Pulmonary arterial hypertension carries a high maternal mortality rate in the peripartum period. Pulmonary hypertension may arise as a complication of portal hypertension with poor patient survival.

CASE: A young primigravida with chronic autoimmune hepatitis and portal hypertension presented at 26 4/7 weeks of gestation with contractions and bleeding. Within 48 hours, an 892-g female fetus was delivered vaginally without complications. On postpartum day 2, the mother was found on the floor by her bed. Although initially responsive, within minutes she was unresponsive and resuscitation was unsuccessful. Postmortem examination showed cirrhosis and plexogenic pulmonary arteriopathy.

CONCLUSION: Increased awareness of pulmonary hypertension as a complication of portal hypertension and a high index of clinical suspicion are necessary to diagnose pregnant women with this condition and provide appropriate prenatal counseling and peripartum intervention.

(Obstet Gynecol 2007;110:501–3)

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Pulmonary hypertension is an under-recognized complication of portal hypertension. We present an individual with known autoimmune hepatitis with cirrhosis and portal hypertension where underlying pulmonary hypertension was identified after her postpartum sudden death. Pulmonary hypertension may present in a subtle manner, but is important to appreciate in this high-risk obstetric patient population.

CASE

A young primigravida with a 10-year history of autoimmune hepatitis with chronic thrombocytopenia presented to the hospital at 26 4/7 weeks of gestation with contractions and bleeding. Before her pregnancy, she was a noncompliant transplantation candidate not using birth control. Prenatal care had been initiated at 6 weeks of

Exhibit 60

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Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes

Sandra A. McDonald, Yuwei Fan, William R. Welch, Daniel W. Cramer, Rebecca C. Stearns, Liam Sheedy, Marshall Katler & John J. Godleski

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Correlative polarizing light and scanning electron microscopy for the assessment of talc in pelvic region lymph nodes

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ABSTRACT
Perineal talc use is associated with ovarian carcinoma in many case-control studies. Such talc may migrate to pelvic organs and regional lymph nodes, with both clinical and legal significance. Our goal was to differentiate talc in pelvic lymph nodes due to exposure, versus contamination with talc in the laboratory. We studied 22 lymph nodes from ovarian tumor patients, some of which had documented talc exposure, to quantify talc using digestion of tissue taken from paraffin blocks and scanning electron microscopy/energy dispersive X-ray analysis (SEM/EDX). Talc particles correlated significantly with surface contamination assessments using polarized light microscopy. After adjusting for surface contamination, talc burdens in nodes correlated strongly with perineal talc use. In a separate group of lymph nodes, birefringent particles within the same plane of focus as the tissues in histological sections were highly correlated with talc particles within the tissue by *in situ* SEM/EDX ($r = 0.80$; $p < 0.0001$). We conclude that since talc can be a surface contaminant from tissue collection/preparation, digestion measurements may be influenced by contamination. Instead, because they preserve anatomic landmarks and permit identification of particles in cells and tissues, polarized light microscopy and *in situ* SEM/EDX are recommended to assess talc in lymph nodes.

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Introduction

In diseases related to foreign particulate exposure, accurate quantification of foreign material in tissue is important to document exposure and to correlate with disease occurrence or severity related to that tissue.[1] The issue is perhaps best appreciated for asbestos and pulmonary mesothelioma and fibrosis.[2] The most comprehensive quantification is obtained by digestion of a tissue sample, which uses much larger amounts of tissue that can be assessed in a histologic tissue section.[1] The procedure can be used to identify and quantify individual fibers by transmission electron microscopy (TEM) or scanning electron microscopy (SEM) and characterize them by energy dispersive x-ray analysis (EDX) to verify that their elemental signatures are compatible with a specific type of asbestos or other foreign material exposure[3] Application of TEM and/or SEM and EDX to tissue sections cut from paraffin blocks also provides quantification when the concentration of particles in tissue is sufficiently high.[4,5] This procedure may also show where the foreign material resides within a tissue section, such as exogenous particles localizing in macrophages within lymph nodes.[6] An estimate of foreign particulate exposure may also be obtained by studying histologic tissue sections under polarized light microscopy, which highlights birefringent material and its size and shape.[7,8] Besides the use of these methods in scientific studies to characterize exposures and disease, these techniques have also been used in medicolegal contexts related to claims of injury from various exposures, including asbestos.[1]

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One exposure of great current medical, public health, and medicolegal importance is the association of ovarian cancers with the use of talc cosmetic products in the genital area. Data related to this association come from epidemiologic studies which identified a clear excess of women with ovarian malignancy who had used talc in their genital area prior to developing cancer, compared to control women.[9–13] The International Agency for Research on Cancer has declared the use of talc (not containing asbestos) in the genital area as possibly carcinogenic (Class 2B) (IARC monograph, 2010).[14] The most recent summary of the epidemiologic data in 2018 found that genital talc use may increase the risk for ovarian carcinoma by about 30%.[15] Although the origin of the hypothesis about talc and ovarian cancer came, in part, from description of talc in ovarian tissue,[16] demonstration that talc is present in the ovarian tissue or the genital tract from women with ovarian cancer has not been a component of the epidemiologic studies, and published data regarding talc in women's pelvic organs is very limited. A study by Heller et al.[17] was done with digestion techniques followed by TEM on ovaries from 24 women having hysterectomy/oophorectomy for reasons other than ovarian malignancy. This study found talc in approximately half the samples, with no obvious correlation with genital talc use history, thereby suggesting to the authors that talc exposure may be relatively ubiquitous across the population. A subset of authors from the present study have previously described a case report[6] in which a woman with serous carcinoma of the ovary, and a history of talc usage in her genital area, was demonstrated to have talc in three of four examined pelvic lymph nodes.

In the study reported here, we assessed talc in a sizable set of lymph nodes of the pelvic region, representing multiple patients. Thus, we expanded on the lymph node analysis in the previous case report[6] as well as the study of non-malignant ovaries by Heller et al.[17] and we examined nodes in 22 patients with various types of ovarian tumors. We included the additional step of an independent polarized light microscopy study on the histological sections for each case; this procedure assessed the quantity and location of birefringent particles in relationship to tissue landmarks. By digesting the lymph node samples, assessing the presence of talc by SEM/EDX, and comparing that data to the findings by light microscopy, we assessed tissue surface contamination as a factor explaining the high talc burden in some cases, as opposed to talc that migrated to the nodes from perineal exposure. We also endeavored, by studying a separate group of lymph node cases, to show that polarized light microscopy is a useful adjunct to *in situ* SEM/EDX, since both preserve anatomic landmarks and can serve as indicators of talc whose source is not due to contamination.

Materials and methods

Twenty-two women with ovarian tumors who had received their care in 2004 and 2005 at the Brigham and Women's Hospital (BWH), and who had participated in larger epidemiologic studies of ovarian cancer in Eastern Massachusetts and New Hampshire, were selected for the study. Women in this series were selected consecutively on the basis of meeting eligibility criteria and not on the basis of whether they had used talc. To be eligible, cases must have had lymph nodes removed from the pelvic region as part of their surgery. Cases were ineligible if the only nodes available contained metastatic disease or if there was only one unaffected node available. Though most of the cases were malignant ovarian neoplasms, two cases (one a borderline tumor and the second a granulosa cell tumor) were included because the study's objective was focused on the quantification of talc in tissue and understanding contamination vs. exposure related findings. Relevant clinical data were available both from the medical record and questionnaires completed by the women that included information on the use of talc in the genital area or as a body powder. The study was approved by the BWH Institutional Review Board and the informed consent signed by the women included permission to study material removed at the time of surgery. This group of women had both digestion studies and light microscopic studies of their lymph nodes. For our purposes, nodes of interest included inguinal, iliac, and paraaortic, and potentially any node of the pelvic region used for sampling and/or staging in ovarian surgical oncology. In some cases, the

designation "pelvic lymph node" with laterality, but without further anatomic specification, was provided with a sample.

Talc is readily visible under polarizing light microscopy, where it may be found as both plates and fibrous forms, and where the particles or fibers are brightly birefringent and often in the size range 1–10 µm. Identification of talc by electron microscopy and energy-dispersive X-ray analysis (EDX), includes the plate-like particulate or fiber-like structure and a spectrum showing magnesium and silicon peaks within 5% of the theoretical atomic ratio of 0.75 and atomic weight percent ratio of 0.649.

For each patient case, we ascertained that an acceptable representative hematoxylin-eosin (H&E)-stained slide was available for the block prior to subsequent steps. Tissue was totally cut from the paraffin block with a cleaned scalpel, heat deparaffinized, and then multiple extractions were done with xylene to remove all residual paraffin. The tissue was weighed, then added to glass centrifuge tubes, and sodium hypochlorite solution was added for digestion over a 24–48 hr period. When digestion was complete, samples were centrifuged and the sediment resuspended in filtered distilled water and vortexed until no sediment was visible. The tubes were centrifuged again and the supernatant aspirated. Sediments were resuspended in 25% ethanol, mixed by vortexing and filtered through a 13 mm, 0.2 µm Millipore filter. Tubes were washed twice with 25% ethanol and filtered. Filters were dried in a desiccator and were mounted on a carbon planchette.

Samples were analyzed in a scanning electron microscope (Leo 1460VP) equipped with an EDX spectrometer (Oxford instruments with Inca software) or an Hitachi SU6600 field emission scanning electron microscope with Oxford EDX (Xmax 50SDD EDX detector) and Oxford instrumentation software (Aztec 3.3). At 2000x magnification, 200 particles or 100 random fields were analyzed for each case, whichever came first. Using various parameters, including the number of talc particles identified by their chemical composition, the area of each microscopic field times the number of fields examined, and the overall filter area, an estimate for the total number of talc particles in the specimen was calculated.

Because fat, fibrous tissue, and lymph node contributed to the weight of the material used for digestion and because there were differences in birefringent particle distribution patterns of the tissue surface, fat and fibrous tissue, and lymph node, a more accurate approach was needed by which we could estimate the contributions of the separate locations. Tissues on all slides were digitized. Using NIH Image J analysis software (an open source image processing program, www.imagej.com), the total areas (cm^2) of the tissue on the slides for each case were calculated, as well as the respective components of lymph node and fibroadipose (soft) tissue, with the sum of these areas adding up to the total tissue area. These figures were then multiplied by 0.25 cm (a typical thickness for tissue in paraffin cassettes from which the digested tissues were derived) to obtain total specimen volumes for the total tissue, and for the lymph node and soft tissue components. The total number of talc particles identified in the digestate by SEM was then divided by the total tissue volume to obtain the number of talc particles per unit volume (cm^3).

H&E slides of intact lymph node tissue corresponding to each digested paraffin sample were analyzed with an Olympus BH-2 light microscope equipped with polarizing filter capabilities (analyzer and rotating polarizer with specimen slide in between). Each slide was scanned systematically and completely at 200x magnification under polarized light. Slides typically contained one to several lymph node profiles with adherent fibroadipose tissue. Birefringent particles visually consistent with talc (typically 1–10 µm with birefringence) were counted that were located within the lymph node parenchyma and sinuses, and a separate count was made of particles in fibroadipose (soft) tissue, i.e. not within the lymph nodes proper. The counts of these two components were added to get the total count. Particles within fibroadipose tissue were counted only if they were at least one 400x (high-power) field away from the surface, so that obvious surface contamination was not included in the counts. The birefringent particles present within lymph nodes were taken to indicate clinically significant talc that migrated there through the lymphatic system. Birefringent particles on the physical surface of the tissues were not counted for these analyses but instead assessed as described below.

Using the aforementioned image analysis data which provided the areas (cm^2) for the total tissue on the slide as well as the lymph node and soft tissue components, for each slide, the respective tissue volumes were calculated by multiplying the areas by 4 µm (4×10^{-4} cm), a standard tissue section thickness on glass slides. The number of birefringent particles per unit volume were then calculated (through simple division) for each tissue component and for the overall tissue. This meant that the volume correction factor between tissue blocks and tissue slides was approximately 625 (0.25 cm thickness of tissue in blocks vs. 4 µm thickness of slides).

Additionally, for each of the 22 cases, a semi-quantitative visual estimate of surface contamination was made. This was done by observing the quantity and pattern of all polarizable material (typically birefringent particles of 1–10 µm, plus larger material such as paper, organic fibers, and other debris) that were present along the specimen edge and/or within one 400x (high power microscopic field) width from it. The objective here was to measure the degree to which the specimen surfaces might have been contaminated by physical manipulation during the acquisition and handling steps of the specimen in the Pathology department. Our estimate scores ranged from 0 to 3 and the criteria for the scoring was as follows (see Figure 1): 0, no polarizable material along surface; 1, occasional foreign particulates, rarely forming small clusters; 2, moderate numbers of surface particulates, forming occasional clusters or surface patches more numerous than in score 1; 3, frequent patches of particulates along with confluent stretches of contamination along the surface. Typically, such contamination was seen along the fibroadipose tissue surface with the nodal tissue interior to that. The contamination consisted typically of a mix of larger debris consistent with paper, along with smaller birefringent particulates similar to those seen and described in tissue sections (Figure 1). All contamination scores were done by a pathologist (JJG) in a blinded fashion (SEM and clinical data were unavailable at the time of scoring). A randomly chosen subset of the same cases was independently scored by a second pathologist (SM), also in a blinded fashion, to confirm successfully that the review standards agreed, and thus the scoring standards were being applied consistently.

Subsequent statistical analysis for the 22 cases was handled as follows: Talc counts were log transformed to create normal distributions. Spearman correlations were calculated to assess the relationship between potential contamination on the talc counts and each continuous variable, and partial correlations were used to examine the relationships between talc counts, adjusted for contamination. Linear regression was used to calculate crude and contamination-adjusted talc/total volume geometric means and 95% confidence intervals.

Also, as part of this report, we studied a second group of 19 lymph node specimens from 10 ovarian carcinoma cases. The 10 cases were consults of authors JJG and WW, which were de-identified, i.e. reported here without any patient identifiers, including the 18 recognized HIPAA identifiers.[18] All 19 tissue specimens had histologic slides and corresponding paraffin blocks available. In this component of the study, we assessed the relationship of the numbers of birefringent particles in the lymph node parenchyma in histological sections, and talc particles found by *in situ* SEM/EDX at deeper levels in the tissue blocks corresponding to those sections. Digestion was not performed on these cases; nor was information available on their talc exposure. Birefringent particles in the lymph nodes were exhaustively quantified by light microscopy as previously described (particles counted in respective lymph node and soft tissue components, added to a total count for each slide). The histologic slides typically contained from one to several lymph node profiles, each with adherent fibroadipose tissue. Counting was done without regard to the number of profiles; i.e. an aggregate count was obtained across all lymph node tissue on a slide.

The tissue blocks were handled with a procedure for *in situ* SEM/EDX distinct from the tissue digestion and filter analysis by SEM described in the previous component of the study. This *in situ* procedure was first described by Thakral and Abraham[4] for assessment of particulate materials in paraffin-embedded tissue. In the study reported here, the blocks were handled with particle-free gloves on pre-cleaned surfaces and sectioned removing ~30 micrometers of tissue

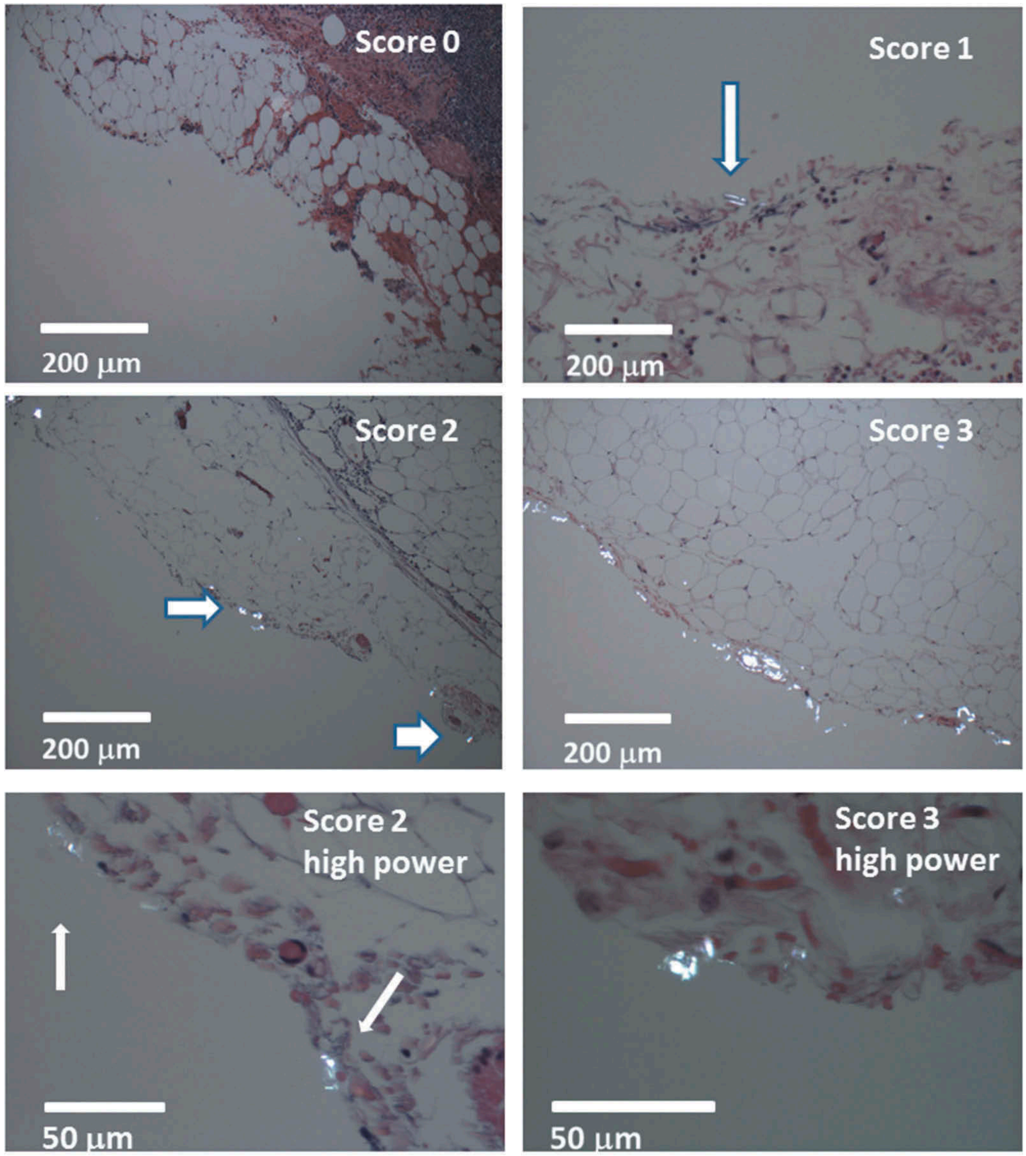

Figure 1. Tissue surface contamination score semi-quantitative grading. As shown especially in the two high-power images at bottom, the contamination material consisted typically of larger debris consistent with paper, along with smaller birefringent particulates. Surface contamination was typically found along the fibroadipose tissue surface, with lymph node tissue located underneath. Grading scheme is as follows: **Score 0**: no polarizable material along surface. **Score 1**: occasional birefringent particulates (arrows), rarely forming small clusters. **Score 2**: moderate numbers of surface birefringent particulates (arrows), forming occasional clusters or surface patches more numerous than in score 1. **Score 3**: frequent patches of particulates along with confluent stretches of contamination along the surface. (All images under polarizing light microscopy, H&E staining, all 100x except 400x [original magnification] in the bottom two images which respectively show score 2 and 3).

and paraffin using a rotary microtome with a new, clean stainless-steel blade. This sectioning was intended to remove any surface contamination from previous storage and handling. After the fresh surface was exposed, the block surfaces were washed in distilled, deionized water for 30 seconds to remove soluble surface materials such as sodium chloride and sodium phosphates used in processing for histology. The blocks were mounted for SEM examination and always kept in closed containers to limit any lab contamination. These tissue surfaces were studied with a Hitachi SU6600 field emission SEM with an Oxford EDX with Aztec version 2.0 to 3.3 software, and EDX detector model X-Max 50 SDD. The backscatter mode of the microscope highlighted mineral particles within the tissues. Areas of the tissue at the sectioned block surface were

examined at relatively low magnification 200-500x, and when particles were seen, they were then examined at higher magnification for morphological characteristics and to carry out spectral analysis on each particle found. Electron beam penetration depth under the conditions used was estimated to be 2.5 µm, with an analysis range of 0.5–2.5 µm. Of note, under *in situ* SEM the interior tissue and exterior tissue surfaces were readily distinguishable; this distinction was important for our study. In particular, as subsequent discussion will show, it was important to avoid analyzing surface particulates and instead analyze those inside the tissue. Having a scanned photocopy of the light microscopic slide and the block surface available for reference when performing SEM/EDX helped in navigating the anatomic landmarks, including surface vs. tissue interior location. We subsequently carried out an auxiliary part of this study, in which surface contamination of tissue slides was assessed using two of the cases that had this finding. The surface particles were assessed by *in situ* SEM/EDX to determine the identity (i.e. chemical composition) of the surface contamination.

For this second part of the study, linear regression analyses, with the generation of a coefficient of determination (r) goodness-of-fit value, were done between three statistical pairings: total birefringent particles by light microscopy vs. *in situ* SEM/EDX talc counts, lymph node birefringent particles vs. *in situ* SEM/EDX talc count, and fibroadipose tissue birefringent particles vs. *in situ* SEM/EDX talc counts. Our hypothesis was that the first two pairings would be correlated but the last one would not. The inclusion of multiple specimens from some of the patients meant that the 19 data points (specimens) were not truly independent of each other from the perspective of the population. However, from a statistical point of view, this was justified because, in this phase of our study, the purpose was an evaluation of methods and data related to the samples themselves, and not the population from which the samples were drawn.

Results

Digestion study

Table 1 shows characteristics of the 22 subjects enrolled in the BWH node digestion study, arrayed (least to greatest) by the amount of talc (by digestion) per cm^3 tissue volume. Fourteen (64%) of the women had invasive serous ovarian carcinoma of the ovary, which in one case was mixed with endometrioid carcinoma. Nineteen of the 22 nodes (86%) were external iliac, with 11/19 (58%) from the right side. The age range of the women was 38–73 with a median of 56; 10 (45%) had used talc in their genital area and 16 (73%) had used it as a body powder. There was considerable variation in total talc counts seen after digestion of the nodes. There was also considerable variation in birefringent particle counts in the nodal components, as well as corresponding counts per cm^3 tissue volume (see column totals where pertinent). The number and proportion of nodes with 0, 1, 2, and 3 surface contamination scores were: 4(18%), 7(32%), 7(32%), and 4 (18%).

Of note, cases 4, 9, and 13 had no clinical exposure history, and yet all had high contamination scores (either 2 or 3) and corresponding moderate to high talc counts per cm^3 tissue volume, thus highlighting a role for contamination in their digestion results. In contrast, cases 10 and 18 had clinical **exposure, but** zero contamination scores (i.e. no visible surface contamination); they also had significant talc counts per cm^3 tissue volume, indicating that in the absence of surface contamination, clinical exposure yields significant talc counts using digestion. Case 18 can also be contrasted with cases 19–22, which had the four highest talc counts per cm^3 tissue volume (Table 1), and all of which had high levels of surface contamination.

Table 2 shows Pearson and partial correlations among the various quantitative measurements related to talc and birefringent particles. The degree of surface contamination (0–3 score) as it correlates with other measures of talc and birefringent particles within the node is shown in the right-most column. The surface contamination score was significantly correlated with: the total talc particle count by digestion ($r = 0.43$, $p = 0.05$); with birefringent particle counts by light microscopy in the soft tissue (fibroadipose) component ($r = 0.53$, $p = 0.01$); with total talc per cm^3 tissue volume by SEM/EDX ($r = 0.57$, $p = 0.006$); and with birefringent particle counts in fibroadipose tissue per cm^3 fibroadipose volume ($r = 0.51$, $p = 0.01$). The remainder of correlations and p values in Table 2 represent those for partial correlations

Table 1. Clinical data and talc digestion and light microscopic data among the first patient group (BWH cases).

Case number	Tumor histology	Node*	Component volume (cm^3) Total	Node	Fat	Age	Talc use Genital	Body	Total talc †	Talc/cm^3 of tissue volume	Total birefringence counts†† Total	Node	Fat	Birefringence per component volume (particles/ cm^3) Total	Node	Fat	Surface contamination
1	Endometrioid	REI	0.341	0.195 (57%)	0.146 (43%)	60	No	Yes	844	2,475	3750	1250	2500	11,000	6,375	17,250	1
2	Serous invasive	LP	0.334	0.171 (51%)	0.164 (49%)	53	No	Yes	1608	4,800	1250	625	625	3,737	3,661	3,812	1
3	Serous invasive	LEI	0.308	0.119 (39%)	0.188 (61%)	69	No	Yes	2065	6,705	10625	6250	4375	34,552	52,301	23,271	0
4	Serous invasive	LEI	0.407	0.252 (62%)	0.155 (38%)	38	No	No	4290	10,540	4375	1250	3125	11,187	4,960	20,187	2
5	Clear cell	REI	0.332	0.189 (57%)	0.143 (43%)	54	No	Yes	3965	11,942	15000	12500	2500	45,146	66,286	17,406	0
6	Serous invasive	REI	0.232	0.169 (73%)	0.063 (27%)	50	Yes	No	3378	14,500	1250	625	625	5,387	3,687	9,937	1
7	Endometrioid	REI	0.557	0.392 (70%)	0.165 (30%)	46	No	No	8920	16,000	4375	1250	3125	7,912	3,187	18,937	1
8	Serous invasive	LEI	0.107	0.039 (36%)	0.069 (64%)	49	Yes	Yes	2533	23,562	1250	0	1250	11,687	0	18,375	1
9	Endometrioid	REI	0.533	0.089 (17%)	0.444 (83%)	57	No	No	19,094	35,823	15000	3125	11875	28,103	35,014	26,715	2
10	Granulosa cell	REI	0.237	0.206 (87%)	0.030 (13%)	49	Yes	Yes	20,267	85,600	4,375	3,125	1,250	18,500	15,125	41,375	0
11	Serous invasive	REI	0.107	0.092 (86%)	0.015 (14%)	51	No	No	10,390	97,100	5,000	625	4,375	46,750	6,812	291,687	2
12	Serous invasive	RP	0.026	0.021 (79%)	0.006 (21%)	51	Yes	Yes	2,834	107,300	10,625	5,625	5,000	402,437	269,125	908,750	2
13	Serous invasive	LEI	0.147	0.022 (15%)	0.125 (85%)	68	No	No	16,057	115,030	16,875	1,250	15,625	114,812	56,562	125,125	3
14	Serous invasive	REI	0.219	0.145 (66%)	0.074 (34%)	73	Yes	Yes	30,330	138,500	8,125	1,875	6,250	37,062	12,937	84,437	2
15	Endometrioid	REI	0.506	0.083 (16%)	0.423 (84%)	58	Yes	Yes	73,267	144,800	26,875	12,500	14,375	53,125	151,500	33,937	2
16	Serous borderline	REI	0.147	0.055 (37%)	0.092 (63%)	60	No	Yes	21,409	145,600	11,875	2,500	9,375	80,812	45,437	101,875	1
17	Serous invasive	LEI	0.174	0.123 (71%)	0.051 (29%)	62	Yes	Yes	33,778	194,100	30,625	28,125	2,500	176,000	228,687	49,437	1
18	Serous invasive	LEI	0.323	0.203 (63%)	0.121 (37%)	53	Yes	Yes	67,557	208,200	>125,000	>125,000	625	>387,000	>616,365	3,000	0
19	Serous invasive	LEI	0.052	0.017 (33%)	0.035 (67%)	69	No	Yes	12,661	242,100	11,250	1,250	10,000	215,000	71,875	285,625	3
20	Serous invasive	LEI	0.286	0.185 (65%)	0.101 (35%)	66	Yes	Yes	92,891	325,200	4,375	3,125	1,250	15,312	16,875	12,437	2
21	Endometrioid	REI	0.056	0.039 (70%)	0.017 (30%)	51	No	Yes	85,041	1,518,589	13,750	1,250	12,500	246,875	32,051	735,294	3
22	Serous/ endometrioid	RPA	0.424	0.284 (67%)	0.139 (33%)	69	Yes	Yes	797,171	1,881,500	>62,500	>62,500	1,250	>147,500	>220,062	9,000	3
Median			0.262	0.134	0.111	56			14,359	102,200	10,625	2,188	3,125	41,104	33,533	24,993	

*Location of Node: LEI = Left external iliac; REI = Right external iliac; RPA = Right paraaortic; LP = Left pelvic; RP = Right pelvic
†Total number of talc particles by digestion (calculated)
††Total birefringence counts = particles in field x 625 (see Materials and Methods)
Node refers to lymph node parenchyma areas as measured by Image J software and studied by light microscopy (see Materials and Methods).
Fat refers to fibroadipose soft tissue areas as measured by Image J software and studied by light microscopy

Table 2. Correlations between surface contamination, talc, and age (r and p values).

Variable*	Surface contamination r (p)	Total talc by digestion r (p)	Total birefringent particle counts: Total r (p)	Node r (p)	Fat r (p)	Talc/total volume r (p)	Birefringent particle counts per cm^3 volume: Total r (p)	Node r (p)	Fat r (p)
Total talc by digestion	0.43 (0.05)								
Total birefringent particle counts	0.15 (0.51)	0.67 (0.001)							
Total birefringent particle counts, node	−0.07 (0.77)	0.59 (0.005)	0.81 (<.0001)						
Total birefringent particle counts, fat	0.53 (0.01)	−0.13 (0.58)	0.25 (0.26)	0.07 (0.76)					
Talc/cm^3 volume	0.57 (0.006)	0.87 (<.0001)	0.63 (0.002)	0.47 (0.03)	−0.06 (0.78)				
Birefringent particles per cm^3 total volume	0.33 (0.13)	0.42 (0.06)	0.82 (<.0001)	0.56 (0.008)	0.3 (0.19)	0.68 (0.0007)			
Birefringence per cm^3 node volume	0.07 (0.77)	0.51 (0.02)	0.90 (<.0001)	0.88 (<.0001)	0.18 (0.45)	0.64 (0.003)	0.87 (<.0001)		
Birefringence per cm^3 fat volume	0.51 (0.01)	−0.24 (0.30)	0.003 (0.99)	−0.1 (0.68)	0.61 (0.003)	0.16 (0.48)	0.45 (0.04)	0.13 (0.58)	
Age	0.28 (0.20)	0.26 (0.26)	0.35 (0.12)	0.32 (0.15)	0.16 (0.49)	0.22 (0.33)	0.26 (0.25)	0.36 (0.12)	−0.07 (0.75)

Node = lymph node tissue
Fat = fibroadipose tissue

adjusted for the level of surface contamination. Not unexpectedly, total counts always strongly correlated with counts per cm^3 of relevant tissues: e.g. total talc with total talc per cm^3 tissue volume ($r = 0.87$, $p = 0.001$); total birefringent particle counts in lymph node tissue with birefringent counts per cm^3 lymph node tissue ($r = 0.88$, $p = 0.0001$); and birefringent particle counts in fibroadipose tissue with birefringence counts per cm^3 fibroadipose volume ($r = 0.61$, $p = 0.003$). Talc counts per cm^3 tissue volume correlated with: birefringent particles per cm^3 tissue volume ($r = 0.68$, $p = 0.007$), and lymph node birefringent particles per cm^3 lymph node tissue ($r = 0.64$, $p = 0.003$), but not with fibroadipose birefringent particles per cm^3 fibroadipose tissue. Total birefringent particles per cm^3 tissue volume correlated best with lymph node birefringent particles per cm^3 lymph node tissue ($r = 0.89$, $p = 0.001$). Birefringent particle counts per cm^3 lymph node tissue were not correlated with fibroadipose birefringent particle counts per cm^3 fibroadipose volume. Age was not significantly correlated with any measure of nodal contamination.

Figure 2 and Table 3 illustrates the potential effect of surface contamination on the interpretation of the relationship between total talc (by digestion) per cm^3 tissue volume. Figure 2 illustrates that for any level of surface contamination, those who used talc in the genital area had a higher amount of talc than those who had not used talc genitally. Table 3 quantifies

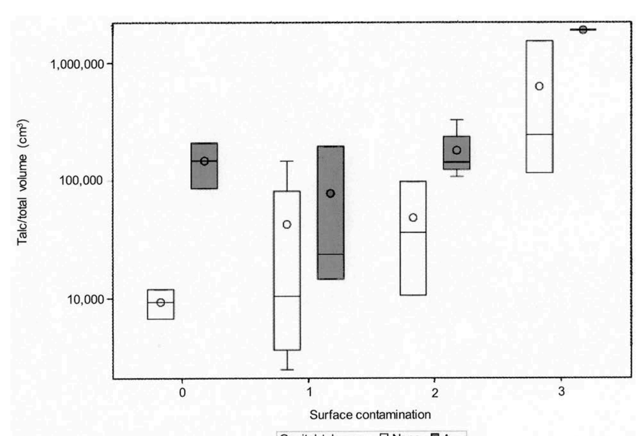

Figure 2. Talc/total volume for genital talc users and non-users by surface contamination This figure shows surface contamination scores (x axis) plotted against talc per tissue volume (y-axis, logarithmic scale), showing that for any level of surface contamination, those who used talc in the genital area had a higher amount of talc than those who had not used talc genitally.

Table 3. Geometric mean talc/total volume by genital talc use.

Talc/total volume	No genital talc use (n = 12) Geometric mean (95% CI)	Any genital talc use (n = 10) Geometric mean (95% CI)	p-value
Crude	35,049 (13,637, 90,079)	131,584 (46,787, 370,070)	0.08
Adjusted for surface contamination	29,926 (15,546, 57,605)	159,056 (77,491, 326,475)	0.004

this effect more precisely and indicates that, overall, the genital talc user had higher talc counts per volume of tissue than those who had not used talc, but the association was of borderline significance. After adjustment for level of surface contamination, the association became significant (p = 0.004) with the level of talc in nodal tissue at least five times higher in those who used talc genitally compared to those who had not.

Figure 3 shows correlative polarizing light microscopy, SEM, and EDX from case 18 in the digestate study (Table 1). Going clockwise from upper left, panel **A** shows polarized light microscopy (H&E, 200x), showing numerous birefringent particles (general size range 1 to 5 μm) within the macrophages of a left external iliac lymph node. This case was near the upper end of the range of particle abundances we observed. Panel **B** shows examples of two particles (labeled 1103 and 1104), identified by SEM on the digestate filter, each <5 μm diameter. Panel **C** shows the spectrum for particle 1103, with an Mg-Si atomic weight ratio of 0.6495, characteristic of talc. The other particle in **B**, 1104, had an Mg-Si ratio within 5% of the theoretical talc value (0.649).

In situ *SEM study*

Table 4 shows data for the second part of the study (19 lymph node specimens from 10 patients). The left-most two columns (case number and block letter) are

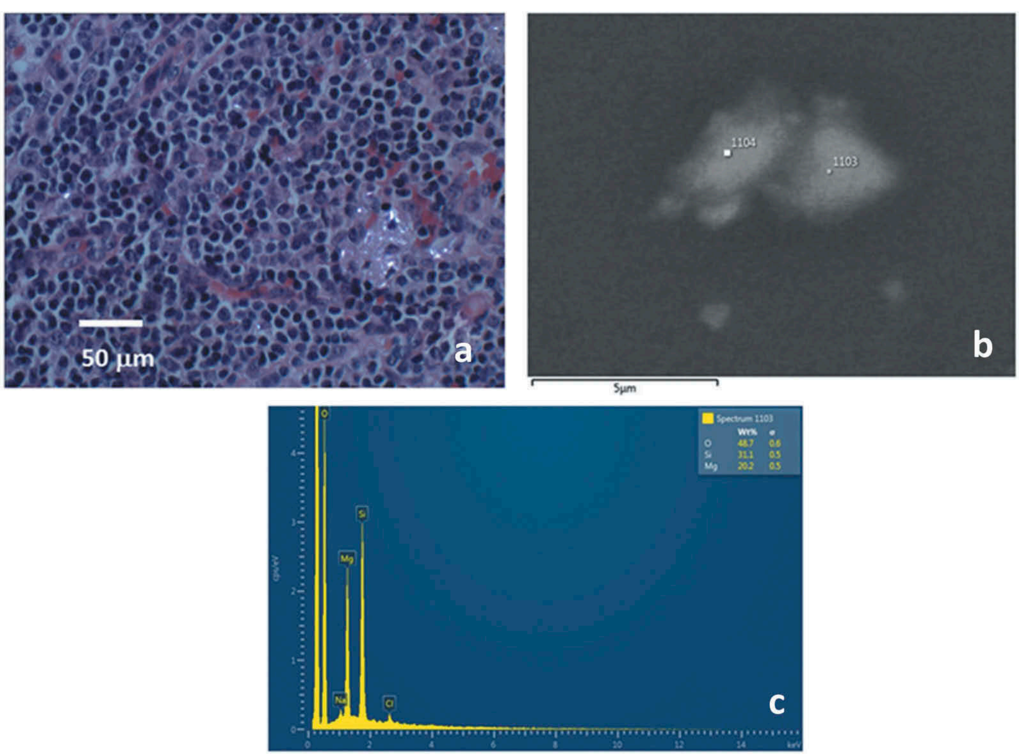

Figure 3. Correlative polarizing light microscopy, SEM, and EDX from case 18 in the digestate study (Table 1). Clockwise from upper left: **a**, Polarizing light microscopy, H&E, 200x, showing numerous birefringent particles (general size range 1 to 5 μm) within the macrophages of a left eternal iliac lymph node. **b**, Two particles (labeled 1103 and 1104), identified by SEM on the digestate filter, each <5 μm diameter. **c**, Spectrum for particle 1103, The Mg-Si atomic weight ratio is 0.6495, characteristic of talc. The other particle in **b**, 1104, had an Mg-Si atomic weight ratio within 5% of the theoretical talc value (0.649).

Table 4. Correlation between light microscopic birefringent particulates and in situ SEM analysis for talc particles.

Case number	Slide letter	Birefringent particles in lymph node tissue (total per slide)	Birefringent particles in surrounding fibroadipose tissue (total per slide)	Total birefringent particles in slide (columns C + D)	Number of talc particles in the block by in situ SEM
1	A	3	5	8	0
	B	55	7	62	5
2	A	5	2	7	9
3	A	2	0	2	0
	B	0	0	0	0
4	A	19	9	28	31
	B	3	1	4	5
5	A	>500	3	>500	65
6	A	6	4	10	0
	B	8	3	11	0
	C	16	4	20	0
7	A	7	3	10	1
	B	1	0	1	0
8	A	>100	3	>100	18
	B	>200	2	>200	43
	C	>100	5	>100	35
	D	>100	7	>100	24
9	A	8	6	14	1
10	A	15	>50	>50	12

In this part of the study, 19 pelvic lymph node slides on 10 ovarian carcinoma patients (with each patient having from one to four node specimens), showed the relationship of the numbers of birefringent particles (by light microscopy) within histological sections (separately categorized in lymph node and fibroadipose tissue components), and talc particles found by SEM/EDX at deeper levels in the tissue blocks corresponding to those sections (right-hand column). In case 9C, the vast majority of the birefringent particles were localized in only one of several lymph nodes visible in the slide. Note that cases with very numerous particle counts by light microscopy are designated simply as greater than a certain threshold.

fully de-identified and serve for identification purposes within the table only. The table shows the relationship of the numbers of birefringent particles by light microscopy within histological sections (separately categorized in lymph node and fibroadipose tissue components), and talc particles found by SEM/EDX on the block surface (following the preparation procedure) corresponding to those sections (right-most column). Consistent with our hypotheses, strong correlations using Spearman correlations were indeed evident between a) lymph node counts by light microscopy and the SEM total talc count ($r = 0.80$, $p < 0.0001$); and b) total particle counts by light microscopy and the SEM total talc count ($r = 0.79$, $p < 0.0001$). Fibroadipose tissue counts by light microscopy did not correlate with SEM total talc counts ($r = 0.32$, p = not significant). In controlling for correlated observations from the same patient, Spearman correlations using one record per case were done for the six patients where more than one lymph node specimen was included in the study (among these patients, the specimen with the highest SEM talc count was the one selected). With this adjustment, strong correlations were still observed using Spearman correlations as evident between a) lymph node counts by light microscopy and the SEM total talc count ($r = 0.69$, $p < 0.03$); and b) total particle counts by light microscopy and the SEM total talc count ($r = 0.74$, $p < 0.01$), Fibroadipose tissue counts by light microscopy did not correlate with SEM total talc counts ($r = 0.16$, p = not significant).

Figure 4 shows correlative polarizing light microscopy, *in situ* SEM, and EDX on case 9C from Table 4. Going clockwise from lower left, panel **A** shows numerous birefringent particles under polarized light microscopy (H&E, 400x) within the macrophages of a left external iliac lymph node. Panel **B** shows low-power backscattered electron imaging under SEM with several positive particles. Panel **C** shows an enlarged (cropped) view of the lower right-hand part of panel B. Three particles are labeled – 44, 45, and 46. Panel **D** shows the spectrum for particle 45, which showed an Mg-Si ratio of 0.643. Particle 44 was also within the 5% of the theoretical value of 0.649 and so was considered talc as well. Particle 46 had an Mg-Si ratio of 0.610, which falls just outside the 0.649 ± 5% range for talc, and so it was considered a nonspecific magnesium silicate.

A review of the non-talc particles found by *in situ* SEM in the 10 patients in Table 4 showed an aggregated total of 310, which based on their chemical composition would be regarded as likely birefringent. Of these, the most common were magnesium silicates outside the 5% theoretical range of the Mg-Si atomic weight spectral ratio for talc (113 total particles or 36%), aluminum silicates with or without magnesium (91 total particles or 29%), and calcium without phosphate (41, or 13%), with others accounting for the remaining 22%. Non-fibrous, non-talc silicates are known to have a longer dissolution time than talc in physiologic conditions; the dissolution time for talc is approximately 8 years for a 1 μm particle.[19] Thus, the component of non-talc silicates in pelvic tissues could proportionally rise over sufficient

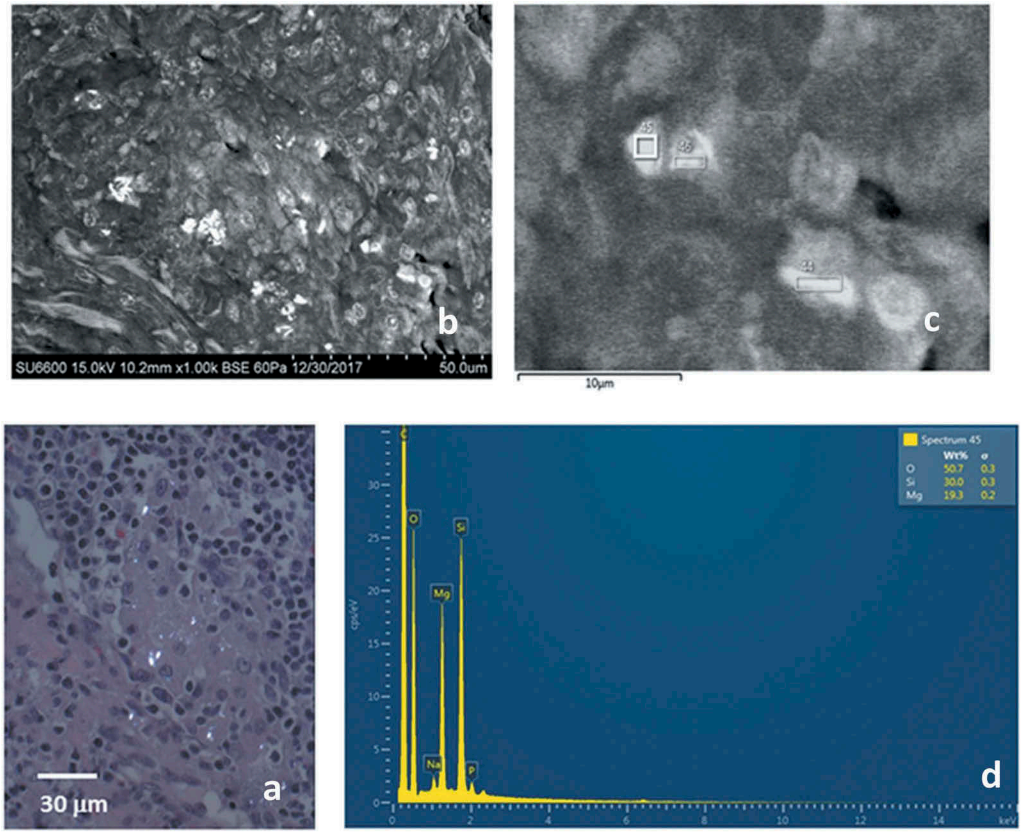

Figure 4. Correlative polarizing light microscopy, in situ SEM, and EDX on case 8C from Table 4. Clockwise from lower left: **a**, Numerous birefringent particles under polarized light microscopy (H&E, 400x) within the macrophages of a left external iliac lymph node. **b**, Low-power backscattered electron imaging under SEM with several positive particles. **c**, Enlarged (cropped) lower right-hand portion of **b**. Three particles are labeled – 44, 45, and 46. **d**, Spectrum for particle 45, which showed an Mg-Si atomic weight ratio of 0.643. Particle 44 was also within the 5% of the theoretical value of 0.649 and so can be considered talc as well. Particle 46 had an Mg-Si atomic weight ratio of 0.610, which falls just outside the 5% range for talc and so can be considered a nonspecific magnesium silicate.

elapsed time (years), even if the original exposure to talc was heavy.

To provide final evidence for our hypothesis that talc is an important part of specimen surface contamination, two authors (SM and JG) re-reviewed the 19 slides from the second part of the study (*in situ* SEM). The goal was to find cases in this group with surface contamination. We did not find any with a score of 3, but two cases (1B and 7A from Table 4) were chosen that, respectively, had contamination scores of 2 and 1 (with 100% agreement by pathologists SM and JG), and substantial amounts of evaluable surface area. On polarizing light microscopy, these cases showed a mixture of larger paper debris fragments and smaller (1–10 µm) birefringent particulates along the surface similar to those previously seen for many Table 1 cases., Respectively, for 1B and 7A, 13 and 5 small birefringent particulates were found by thorough examination of their surfaces in addition to larger paper debris. SEM of the tissue surface for block 1B (35 mm^2 analysis area) showed a total of 5 talc particles, and for 7A showed 1 talc particle (50 mm^2 analysis area). Given the 2.5 µm effective section thickness (electron beam analysis depth) and these relatively small surface areas, these SEM talc particle counts are significant, and are consistent with the light microscopic review. Thus, this portion of the study directly showed that surface contamination particles were talc, whereas previously, this had only been strongly implied by the results in Table 1. (See supplementary figure S1). In addition to the talc particles, 44 other exogenous particles were found across tissue surfaces of these two cases by SEM/EDX: 27 external mineral (mainly Si in combination with Mg and/or Al), 6 non-talc Mg-Si minerals, and 11 external metal.

Discussion

The accurate identification of talc in pelvic tissues is important because it documents exposure by demonstrating the presence of talc in these tissues and provides evidence in support of the role of talc in the epidemiological association with ovarian cancer in case-control studies.[9–13,15] The overall relative risk across the various positive studies is around 1.3, and where tumor histology data have been available for review, several common subtypes (serous carcinoma, endometrioid carcinoma, and serous borderline tumors) are most frequently involved in the association.[11,13]

Talc, when applied to the perineum, is believed to migrate to the upper genital tract, passing through the open tract to the fallopian tubes and eventually reaching the ovaries.[11,16] Talc may also gain access to the lymphatic system as a means of reaching pelvic organs and lymph nodes,[20,21], similar to the route to the pulmonary nodes of talc miners.[22] Lymph nodes of the pelvic region include several anatomic sub-classifications (inguinal, iliac, and paraaortic), with the common theme that they may receive lymphatic efferents from pelvic organs such as the ovaries and perineum and/or secondarily from other lymph nodes in the area. Ovarian carcinoma, especially serous, tends to metastasize early (when just one or two nodes are involved) to paraaortic nodes.[23] Full discussions of the lymphatic drainage/anatomy of the pelvic region are available in the literature.[20,21] Lymph nodes are often sampled during gynecologic surgery for tumor staging and assessment for metastatic disease. However, additional examination of these nodes for talc, especially in settings where genital exposure is known to have occurred, would add insight as to the ability of talc to migrate and lodge within pelvic tissues.

This study supports earlier observations that talc particles, from perineal exposure, can and do migrate to pelvic lymph nodes. Material with the microscopic and spectral features of talc was clearly demonstrated within the lymph node parenchyma in most of our cases, as scattered birefringent particles in the general size range 1–10 μm. Sometimes the material was visible within nodal macrophages, lending strong credence to a lymphatic migration route. Similar particles were also found in the fibroadipose tissue adjacent to lymph nodes, where they may have arrived via the lymphatic system, but more likely resulted from visibly present surface contamination pushed into the underlying fibroadipose tissue.

Our study took the additional critical step of comparing the light microscopic data to SEM digestion data, thereby going beyond the earlier study by Heller et al.[17] in scope, in addition to examining lymph nodes rather than ovaries. Like that earlier paper, we found high talc particle burdens in some digested samples. But because these correlated with contamination scores, we believe that the digestion counts are not fully reflective of clinically relevant talc exposure or its migration in the tissues. Instead, they are influenced by contamination, such as talc introduced by non-surgical gloves used for handling tissue and in the general lab environment during tissue collection and processing in the pathology laboratory. Thus, tissue digestion should not be regarded as a reliable quantification method for talc or contaminants of talc, especially where the collection and processing steps have not been rigidly controlled from the start. The correlation of contamination scores with counts of birefringent particles in fibroadipose tissue suggests that particles adherent to the surface (through contamination) may be pushed into the soft fibroadipose tissue, since it is typically the most peripheral type of tissue, with the nodal tissue usually deeper and encapsulated with a fibrous tissue capsule. The highly variable talc burdens found by digestive analysis and SEM, spanning approximately three orders of magnitude, are consistent with contamination influence, since the latter would be expected to vary considerably between procurement environments. However, this could also be observed in the range of burdens seen in a clinically exposed population with appropriate lab procedures/controls (Table 4).

Even though contamination played a role in total tissue counts, it was still the case that high talc burdens in the lymph nodes, when present, contributed to the SEM digestate results, hence producing the observed correlation between the two. Thus, it is likely that both contamination and clinically significant lymph node talc are reflected in the SEM digestate data. The main

problem in using digestion is that it likely raises the baseline for all patients and groups, thus potentially obscuring clinically significant differences, which would otherwise be observed if contamination were eliminated (as previously mentioned, Table 3 illustrates a robust demonstration of this effect).

By showing strong correlations between particle counts (polarized light microscopy) and *in situ* SEM analysis, the second part of our study demonstrated that the latter alternative is a better method of talc assessment than digestion, because the anatomic landmarks are preserved and surface contamination is not incorporated into the general talc count, as it is with tissue digestion. In combination with other parts of our study, this aspect also showed that the birefringent material in the lymph node tissue, is the clinically significant component related to talc exposure. Surface contamination can still be present, and our demonstration of talc on the surfaces of cases 1B and 7A by *in situ* SEM lent support to the conclusions from the first (digestion) part of the study.

A major strength of our study was the correlative light microscopic and SEM/EDX data for each case, with examination of anatomic locations in the former. This provided a key perspective in the evaluation of the talc burden data that a digestive study alone would not have given. In fact, this study demonstrates the broader principle that correlative histologic review is important in many areas of pathology – especially where digestion procedures are performed, and where the study of anatomic landmarks are needed to complement data from the latter. This is because the tissue is compartmentalized histologically, with different functions and significance for each component, a fact not always recognized by those who digest tissue routinely and use the resulting product completely in analyses such as Western blotting or mutational assays.[24]

Unfortunately, as part of our study, we were not able to also do *in situ* SEM/EDX on the intact tissues used for digestion in the first group of cases (22 patients). However, by showing that birefringent particles within lymph nodes were strongly correlated with the demonstration of talc inside the nodes by *in situ* SEM/EDX, the second part of our study filled that role, and thus 1) material in lymph nodes is likely reflective of the clinical exposure, 2) in this clinical setting and given our results, a substantial proportion of this birefringent material is likely to be talc, 3) surface contamination is common, and so with *in situ* SEM, it is important to discern the anatomic landmarks, and avoid analyzing surface particulates (as shown by our direct demonstration of talc on the surfaces of cases 1B and 7A in our auxiliary study to the cases in Table 4).

In addition to talc, much other commonly found birefringent material, such as that described in the Results section for the SEM analysis, is likely nonspecific particulate material which finds its way into the perineum through general living and hygiene practices. Another important point is that seeing particles by *in situ* microscopy, both light and SEM, requires a relatively large amount of material distributed within the tissues in order to find it. As a demonstration of this principle, Roggli and Pratt[25] showed that finding one asbestos body in a tissue section was indicative of at least 100 fibers per gram of tissue. The calculations we used to estimate particles/cm^3 of tissue volume (Table 1), starting with a count of birefringent particles in tissue sections, illustrate a similar principle.

In the long-studied and debated association between talc exposure and ovarian cancer, our study provides additional evidence that talc may enter pelvic tissues and ultimately be detected and measured in regional lymph nodes, and this relationship became especially strong when clinical use data was considered and surface contamination was corrected for statistically. This adds perspective to the known migratory capabilities and overall biological role/impact of talc. For some of the more heavily exposed cases in the second part of the study, we noticed that the large majority of birefringent material was localized in a single node, among several present on a given slide. This suggested that pelvic drainage/migration pathways for talc may be very specific, and focused on one or relatively few nodes as an endpoint – perhaps consistent with the concept of sentinel nodes in oncologic surgery.[26]

Our findings also suggest that in patients with ovarian cancer, clinicians may want to make broader inquiries into the past and present use

of talc by their patients. Similarly, pathologists may wish to pay greater attention to sampled regional lymph nodes. In addition to the usual study of these nodes for metastases, they may wish to examine macrophages more closely for exogenous particles including by polarized light. A positive finding may trigger clinical inquiries about exposure where it was not previously suspected. Our findings yield important insights as to the ability of talc to migrate to nodes, and under what conditions its identification in nodes and tissues is clinically meaningful and when not.

In conclusion, talc contamination of the surface of surgical pathology specimens is common. Exposure (such as perineal application), whether known clinically or not, often results in significant deposition of talc in the tissues. Correlative light microscopy is needed to assess the possibility of lab contamination, and to determine if talc is truly present in clinically meaningful locations in lymph nodes or other tissues.

Declaration of Interest Statement

The authors declare the following competing financial interest(s): JJG, DC and WW have served as consultants and provided expert testimony in talc and other environmental litigation. SM, YF, RS, MK, and LS report no conflicts of interest.

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References

1. Abraham JL. Analysis of fibrous and nonfibrous particles. In: Rom WN, Markowitz SB, eds. *Environmental and Occupational Medicine. 4th* ed. Philadelphia: Lippincott Williams and Wilkins; 2006:277–297.
2. Roggli VL. Asbestos bodies and nonasbestos ferruginous bodies. In: Roggli VL, Greenberg SD, Pratt PC, eds. *Pathology of Asbestos-Associated Diseases*. Boston: Little Brown; 1992:39–75.
3. McDonald JW, Roggli VL, Churg A, et al. Microprobe analysis in pulmonary pathology. In Ingram P, Shelburne JD, Roggli VL, et al. eds. *Biomedical Applications of Microprobe Analysis*. San Diego: Academic Press; 1999:201–256.
4. Thakral C, Abraham JL. Automated scanning electron microscopy and x-ray microanalysis for in situ quantification of gadolinium deposits in skin. *J Electron Microsc*. 2007;56:181–187. doi:10.1093/jmicro/dfm020.
5. Shelburne JD, Estrada H, Hale M et al. Correlative microscopy and microprobe analysis in pathology. In: Bailey GW, ed., *Proceedings of the 47th Annual Meeting of the Electron Microscopy Society of America*, San Francisco: San Francisco Press; 1989: 900.
6. Cramer DW, Welch WR, Berkowitz RS, et al. Presence of talc in pelvic lymph nodes of a woman with ovarian cancer and long-term genital exposure to cosmetic talc. *Obstet Gynecol*. 2007;110:498–501. doi:10.1097/01.AOG.0000262902.80861.a0.
7. Wolman M. Polarized light microscopy as a diagnostic tool of pathology. *J Histochem Cytochem*. 1975;23:21–50. doi:10.1177/23.1.1090645.
8. McDonald JW, Roggli VL. Demonstration of silica particles in lung tissue by polarizing light microscopy. *Arch Pathol Lab Med*. 1995;119:242–246.
9. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc. *Cancer*. 1982;50:372–376.
10. Cramer DW, Lieberman RF, Ernstoff LT, et al. Genital talc exposure and risk of ovarian cancer. *Int J Cancer*. 1999;81:351–356.
11. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. *Epidemiol*. 2016;27:334–346. doi:10.1097/EDE.0000000000000434.
12. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: the African-American Cancer Epidemiology Study ((AACES). *Cancer Epidemiol Biomarkers Prev*. 2016;25:1411–1417. doi:10.1158/1055-9965.EPI-15-1281.
13. Terry KL, Karageorgi S, Shvetsov YB, et al. Genital powder use and risk of ovarian cancer: a pooled analysis of 8,525 cases and 9,859 controls. *Cancer Prev Res*. 2013;6:811–821. doi:10.1158/1940-6207.CAPR-13-0037.
14. IARC (International Agency for Research on Cancer). *Monograph 93-8C*. 2010:277–413. Lyon, France: World Health Organization.
15. Penninkalimpi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiol*. 2018;29:41–49. doi:10.1097/EDE.0000000000000745.
16. Henderson WJ, Joslin CAF, Turnbull AC, et al. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw*. 1971;78:266–272.
17. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol*. 1996;174:1507–1510.

18. https://www.atlanta.va.gov/Docs/HIPAA_Identifiers.pdf
19. Jurinski JB, Rimstidt JD. Biodurability of talc. *Am Mineralologist*. 2001;86:392–399. doi:10.2138/am-2001-0402.
20. Wolfram-Gabel R. Anatomy of the pelvic lymphatic system. *Cancer Radiotherapie*. 2013;17:549–552. doi:10.1016/j.canrad.2013.05.010.
21. Kubik S, Todury G, Ruttimann A, et al. Nomenclature of the lymph nodes of the retroperitoneum, the pelvis and the lower extremity. In: Ruttimann A, ed. *Progress in Lymphology*. Stuttgart: Georg Thieme Verlag; 1967:52–56.
22. Roggli VL, Benning TL. Asbestos bodies in pulmonary hilar lymph nodes. *Mod Pathol*. 1990;3:513–517.
23. Haller H, Mamula O, Krasevic M, et al. Frequency and distribution of lymph node metastases in epithelial ovarian cancer. *Int J Gynecol Cancer*. 2011;21:245–250.
24. McDonald SA. Principles of research tissue banking and specimen evaluation from the pathologist's perspective. *Biopreserv Biobank*. 2010;8:197–201. doi:10.1089/bio.2010.0018.
25. Roggli VL, Pratt PC. Numbers of asbestos bodies on iron-stained tissue sections in relation to asbestos body counts in lung tissue digests. *Hum Pathol*. 1983;14:355–361.
26. Leitje JAP, Valdes Olmos RA, Nieweg OE, et al. Anatomical mapping of lymphatic drainage in penile carcinoma with SPECT-CT: implications for the extent of inguinal lymph node dissection. *Eur Urol* 2008; 54:885-890. doi:10.1016/j.euroro.2008.04.094.